Exhibit 3

NICKEL AND NICKEL COMPOUNDS

Nickel and nickel compounds were considered by previous IARC Working Groups in 1972, 1975, 1979, 1982, 1987, and 1989 (IARC, 1973, 1976, 1979, 1982, 1987, 1990). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agents

Synonyms, trade names, and molecular formulae for nickel, nickel alloys, and selected nickel compounds are presented in Table 1.1. This list is not exhaustive, nor does it necessarily reflect the commercial importance of the various nickel-containing substances, but it is indicative of the range of nickel alloys and compounds available, including some compounds that are important commercially, and those that have been tested in biological systems. Several intermediary compounds occur in refineries that cannot be characterized, and are thus not listed.

1.2 Chemical and physical properties of the agents

Nickel (atomic number, 28; atomic weight, 58.69) is a metal, which belongs to group VIIIB of the periodic table. The most important oxidation state of nickel is +2, although the +3 and +4 oxidation states are also known (Tundermann *et al.*, 2005). Nickel resembles iron, cobalt, and copper in its chemical properties. However, unlike cobalt and iron, it is normally only stable in aqueous solution in the + 2 oxidation state (Kerfoot, 2002). Selected chemical and physical properties for nickel and nickel compounds, including solubility data, were presented in the previous *IARC Monograph* (IARC, 1990), and have been reported elsewhere (ATSDR, 2005).

1.3 Use of the agents

The chemical properties of nickel (i.e. hardness, high melting point, ductility, malleability, somewhat ferromagnetic, fair conductor of heat and electricity) make it suitable to be combined with other elements to form many alloys (NTP, 2000; Tundermann *et al.*, 2005). It imparts such desirable properties as corrosion resistance, heat resistance, hardness, and strength.

Nickel salts are used in electroplating, ceramics, pigments, and as intermediates (e.g. catalysts, formation of other nickel compounds). Sinter nickel oxide is used in nickel catalysts in the ceramics industry, in the manufacture of alloy steel and stainless steel, in the manufacture of nickel salts for specialty ceramics, and in the manufacture of nickel–cadmium (Ni–Cd) batteries, and nickel–metal-hydride batteries. Nickel sulfide is used as a catalyst in

Table 1.1 Chemical names (CAS names are given in italics), synonyms, and molecular formulae or compositions of nickel, nickel alloys and selected nickel compounds

Chemical name	CAS Reg. No.	Synonyms	Formula
Metallic nickel and nickel alloys			
Nickel	7440-02-0	C.I. 77775; Nickel element	Ni
Ferronickel	11133-76-9	*Iron alloy (base), Fe, Ni*; nickel alloy (nonbase) Fe, Ni	Fe, Ni
Nickel aluminium alloys	61431-86-5 37187-84-1	*Raney nickel*; Raney alloy	NiAl
Nickel oxides and hydroxides			
Nickel hydroxide (amorphous)	12054-48-7 (11113-74-9)	Nickel dihydroxide; nickel (II) hydroxide; nickel (2+) hydroxide; *nickel hydroxide (Ni(OH)2)*; nickelous hydroxide	$Ni(OH)_2$
Nickel monoxide	1313-99-1 11099-02-8 34492-97-2	Black nickel oxide[a]; green nickel oxide; mononickel oxide; nickel monooxide; nickelous oxide; *nickel oxide (NiO)*; nickel (II) oxide; nickel (2+) oxide *Bunsenite (NiO)*	NiO
Nickel trioxide	1314-06-3	Black nickel oxided; dinickel trioxide; nickelic oxide; nickel oxide; nickel (III) oxide; *nickel oxide (Ni_2O_3)*; nickel peroxide; nickel sesquioxide	Ni_2O_3
Nickel sulfides			
Nickel disulfide	12035-51-7 12035-50-6	*Nickel sulfide (NiS_2)* *Vaesite (NiS_2)*	NiS_2
Nickel sulfide (amorphous)	16812-54-7 (11113-75-0)	Mononickel monosulfide; nickel mono-sulfide; nickel monosulfide (NiS); nickelous sulfide; nickel (II) sulfide; nickel (2+) sulfide;	NiS
	1314-04-1 (61026-96-8)	*Nickel sulfide (NiS)* *Millerite (NiS)*	
Nickel subsulfide	12035-72-2	Nickel sesquisulfide; nickel subsulfide (Ni_3S_2); *nickel sulfide (Ni_3S_2)*; trinickel disulfide	Ni_3S_2
	12035-71-1	*Heazlewoodite (Ni_3S_2)*; Khizlevudite	
Pentlandite	53809-86-2	Pentlandite ($Fe_9Ni_9S_{16}$)	Fe9Ni9S16
	12174-14-0	Pentlandite	$(Fe_{0.4-0.6}Ni_{0.4-0.6})_9S_8$

Table 1.1 (continued)

Chemical name	CAS Reg. No.	Synonyms	Formula
Nickel salts			
Nickel carbonate	3333-67-3	*Carbonic acid, nickel (2+) salt (1:1)*; nickel carbonate (1:1); nickel (II) carbonate; nickel (2+) carbonate; nickel carbonate ($NiCO_3$); nickel (2+) carbonate ($NiCO_3$); nickel monocarbonate; nickelous carbonate	$NiCO_3$
Basic nickel carbonates	12607-70-4	Carbonic acid, nickel salt, basic; nickel carbonate hydroxide ($Ni_3(CO_3)(OH)_4$); *nickel, (carbonato(2-)) tetrahydroxytri-*	$NiCO_3.2Ni(OH)_2$
	12122-15-5	*Nickel bis(carbonato(2-)) hexahydroxypenta-*; nickel hydroxycarbonate	$2NiCO_3.3Ni(OH)_2$
Nickel acetate	373-02-4	*Acetic acid, nickel (2+) salt*; nickel (II) acetate; nickel (2+) acetate; nickel diacetate; nickelous acetate	$Ni(OCOCH_3)_2$
Nickel acetate tetrahydrate	6018-89-9	*Acetic acid, nickel (+2) salt, tetrahydrate*	$Ni(OCOCH_3)_2.4H_2O$
Nickel ammonium sulfates	15-699-18-0	Ammonium nickel sulfate ($(NH_4)_2Ni(SO_4)_2$); nickel ammonium sulfate ($Ni(NH_4)_2(SO_4)_2$); *sulfuric acid, ammonium nickel (2+) salt (2:2:1)*	$Ni(NH_4)_2(SO_4)_2$
Nickel ammonium sulfate hexahydrate	25749-08-0	Ammonium nickel sulfate ($(NH_4)_2Ni_2(SO_4)_3$); *sulfuric acid, ammonium nickel (2+) salt (3:2:2)*	$Ni_2(NH_4)_2(SO_4)_3$
	7785-20-8	Ammonium nickel (2+) sulfate hexahydrate; ammonium nickel sulfate ($(NH_4)_2Ni(SO_4)_2$); diammonium nickel disulfate hexahydrate; diammonium nickel (2+) disulfate hexahydrate; nickel ammonium sulfate ($Ni(NH_4)_2(SO_4)_2$) hexahydrate; nickel diammonium disulfate hexahydrate; *sulfuric acid, ammonium nickel (2+) salt (2:2:1), hexahydrate*	$Ni(NH_4)_2(SO_4)_2.6H_2O$
Nickel chromate	14721-18-7	*Chromium nickel oxide ($NiCrO_4$)*; nickel chromate ($NiCrO_4$); nickel chromium oxide ($NiCrO_4$)	$NiCrO_4$
Nickel chloride	7718-54-9	Nickel (II) chloride; nickel (2+) chloride; *nickel chloride ($NiCl_2$)*; nickel dichloride; nickel dichloride ($NiCl_2$); nickelous cholride	$NiCl_2$
Nickel chloride hexahydrate	7791-20-0	*Nickel chloride (NiCl2) hexahydrate*	$NiCl_2.6H_2O$
Nickel nitrate hexahydrate	13478-00-7	Nickel (2+) bis(nitrate)hexahydrate; nickel dinitrate hexahydrate; nickel (II) nitrate hexahydrate; nickel nitrate (Ni(NO3)2) hexahydrate; nickelous nitrate hexahydrate; *nitric acid, nickel (2+) salt, hexahydrate*	$Ni(NO_3)_2.6H_2O$
Nickel sulfate	7786-81-4	Nickel monosulfate; nickelous sulfate; nickel sulfate (1:1); nickel (II) sulfate; nickel (2+) sulfate; nickel (2+) sulfate (1:1); nickel sulfate ($NiSO_4$); *sulfuric acid, nickel (2+) salt (1:1)*	$NiSO_4$
Nickel sulfate hexahydrate	10101-97-0	*Sulfuric acid, nickel (2+) salt (1:1), hexahydrate*	$NiSO_4.6H_2O$
Nickel sulfate heptahydrate	10101-98-1	*Sulfuric acid, nickel (2+) salt (1:1), heptahydrate*	$NiSO_4.7H_20$

Table 1.1 (continued)

Chemical name	CAS Reg. No.	Synonyms	Formula
Other nickel compounds			
Nickel carbonyl	13463-39-3	*Nickel carbonyl ($Ni(CO)_4$), (T-4)-*; nickel tetracarbonyl; tetracarbonylnickel; tetracarbonylnickel (0)	$Ni(CO)_4$
Nickel antimonide	12035-52-8	*Antimony compound with nickel (1:1)*; nickel antimonide (NiSb); nickel compound with antimony (1:1); nickel monoantimonide	NiSb
	12125-61-0	*Breithauptite (SbNi)*	
Nickel arsenides	27016-75-7	*Nickel arsenide (NiAs)*	NiAs
	1303-13-5	Nickeline; *nickeline (NiAs)*; niccolite	NiAs
	12256-33-6	*Nickel arsenide ($Ni_{11}As_8$)*; nickel arsenide tetragonal	$Ni_{11}As_8$
	12044-65-4	*Maucherite ($Ni_{11}As_8$)*; Placodine; Temiskamite	$Ni_{11}As_8$
	12255-80-0	*Nickel arsenide (Ni_5As_2)*; nickel arsenide hexagonal	Ni_5As_2
Nickel selenide	1314-05-2	Nickel monoselenide; *nickel selenide (NiSe)*	NiSe
	12201-85-3	Maekinenite; *Makinenite (NiSe)*	
Nickel subselenide	12137-13-2	*Nickel selenide (Ni_3Se_2)*	Ni_3Se_2
Nickel sulfarsenide	12255-10-6	*Nickel arsenide sulfide (NiAsS)*	NiAsS
	12255-11-7	*Gersdorffite (NiAsS)*	
Nickel telluride	12142-88-0	Nickel monotelluride; *nickel telluride (NiTe)*	NiTe
	24270-51-7	*Imgreite (NiTe)*	
Nickel titanate	12035-39-1	Nickel titanate(IV); nickel titanate (Ni-TiO3); *nickel titanium oxide (NiTiO3)*; nickel titanium trioxide	$NiTiO_3$
Chrome iron nickel black spinel	71631-15-7	CI: 77 504; *CI Pigment Black 30*; nickel iron chromite black spinel	$(Ni,Fe)(CrFe)_2O_4$ NS
Nickel ferrite brown spinel	68187-10-0	*CI Pigment Brown 34*	$NiFe_2O_4$
Nickelocene	1271-28-9	Bis(η5-2,4-cyclopentadien-1-yl)nickel; di-π-cyclopentadienylnickel; dicyclopentadienyl-nickel; bis(η5-2,4-cyclopentadien-1-yl)-nickel	π-(C5H5)2Ni

[a] In commercial usage, 'black nickel oxide' usually refers to the low-temperature crystalline form of nickel monoxide, but nickel trioxide (Ni_2O_3), an unstable oxide of nickel, may also be called 'black nickel oxide'.

the petrochemical industry or as an intermediate in the metallurgical industry.

According to the US Geological Survey, world use of primary nickel in 2006 was 1.40 million tonnes, a 12% increase over 2005. Stainless steel manufacture accounted for more than 60% of primary nickel consumption in 2006 (USGS, 2008). Of the 231000 tonnes of primary nickel consumed in the USA in 2007, approximately 52% was used in stainless and alloy steel production, 34% in non-ferrous alloys and superalloys, 10% in electroplating, and 4% in other uses. End uses of nickel in the USA in 2007 were as follows: transportation, 30%; chemical industry, 15%; electrical equipment, 10%; construction, 9%; fabricated metal products, 8%; household appliances, 8%; petroleum industry, 7%; machinery, 6%; and others, 7% (Kuck, 2008).

1.3.1 Metallic nickel and nickel alloys

Pure nickel metal is used to prepare nickel alloys (including steels). It is used as such for plating, electroforming, coinage, electrical components, tanks, catalysts, battery plates, sintered components, magnets, and welding rods. Ferronickel is used to prepare steels. Stainless and heat-resistant steels accounted for 93% of its end-use in 1986. Nickel-containing steels with low nickel content (< 5%) are used in construction and tool fabrication. Stainless steels are used in general engineering equipment, chemical equipment, domestic applications, hospital equipment, food processing, architectural panels and fasteners, pollution-control equipment, cryogenic uses, automotive parts, and engine components (IARC, 1990).

Nickel alloys are often divided into categories depending on the primary metal with which they are alloyed (e.g. iron, copper, molybdenum, chromium) and their nickel content. Nickel is alloyed with iron to produce alloy steels (containing 0.3–5% nickel), stainless steels (containing as much as 25–30% nickel, although 8–10% nickel is more typical), and cast irons. Nickel–copper alloys (e.g. Monel alloys) are used for coinage (25% nickel, 75% copper), industrial plumbing (e.g. piping and valves), marine equipment, petrochemical equipment, heat exchangers, condenser tubes, pumps, electrodes for welding, architectural trim, thermocouples, desalination plants, ship propellers, etc. Nickel–chromium alloys (e.g. Nichrome) are used in many applications that require resistance to high temperatures such as heating elements, furnaces, jet engine parts, and reaction vessels. Molybdenum-containing nickel alloys and nickel–iron–chromium alloys (e.g. Inconel) provide strength and corrosion resistance over a wide temperature range, and are used in nuclear and fossil-fuel steam generators, food-processing equipment, and chemical-processing and heat-treating equipment. Hastelloy alloys (which contain nickel, chromium, iron, and molybdenum) provide oxidation and corrosion resistance for use with acids and salts. Nickel-based super-alloys provide high-temperature strength and creep, and stress resistance for use in gas-turbine engines (ATSDR, 2005).

Other groups of nickel alloys are used according to their specific properties for acid-resistant equipment, heating elements for furnaces, low-expansion alloys, cryogenic uses, storage of liquefied gases, high-magnetic-permeability alloys, and surgical implant prostheses.

1.3.2 Nickel oxides and hydroxides

The nickel oxide sinters are used in the manufacture of alloy steels and stainless steels.

Green nickel oxide is a finely divided, relatively pure form of nickel monoxide, produced by firing a mixture of nickel powder and water in air at 1000 °C (IARC, 1990). It is used to manufacture nickel catalysts and specialty ceramics (for porcelain enamelling of steel; in the manufacture of magnetic nickel-zinc ferrites used in electric motors, antennas and television tube yokes; and

as a colourant in glass and ceramic stains used in ceramic tiles, dishes, pottery, and sanitary ware).

Black nickel oxide is a finely divided, pure nickel monoxide, produced by calcination of nickel hydroxycarbonate or nickel nitrate at 600 °C; nickel trioxide (Ni_2O_3), an unstable oxide of nickel, may also be called 'black nickel oxide' (IARC, 1990). Black nickel oxide is used in the manufacture of nickel salts, specialty ceramics, and nickel catalysts (e.g. to enhance the activity of three-way catalysts containing rhodium, platinum, and palladium used in automobile exhaust control).

Nickel hydroxide is used as a catalyst intermediate, and in the manufacture of Ni–Cd batteries (Antonsen & Meshri, 2005).

1.3.3 Nickel sulfides

Nickel sulfide is used as a catalyst in petrochemical hydrogenation when high concentrations of sulfur are present in the distillates. The major use of nickel monosulfide is as an intermediate in the hydrometallurgical processing of silicate-oxide nickel ores (IARC, 1990). Nickel subsulfide is used as an intermediate in the primary nickel industry (ATSDR, 2005).

1.3.4 Nickel salts

Nickel acetate is used in electroplating, as an intermediate (e.g. as catalysts and in the formation of other nickel compounds), as a dye mordant, and as a sealer for anodized aluminium.

Nickel carbonate is used in the manufacture of nickel catalysts, pigments, and other nickel compounds (e.g. nickel oxide, nickel powder); in the preparation of coloured glass; and, as a neutralizing compound in nickel-electroplating solutions.

Nickel ammonium sulfate is used as a dye mordant, in metal-finishing compositions, and as an electrolyte for electroplating.

Nickel chloride is used as an intermediate in the manufacture of nickel catalysts, and to absorb ammonia in industrial gas masks.

Nickel nitrate hexahydrate is used as an intermediate in the manufacture of nickel catalysts and Ni–Cd batteries.

Nickel sulfate hexahydrate is used in nickel electroplating and nickel electrorefining, in 'electroless' nickel plating, and as an intermediate (in the manufacture of other nickel chemicals and catalysts) (Antonsen & Meshri, 2005).

1.3.5 Other nickel compounds

The primary use for nickel carbonyl is as an intermediate (in the production of highly pure nickel), as a catalyst in chemical synthesis, as a reactant in carbonylation reactions, in the vapour-plating of nickel, and in the fabrication of nickel and nickel alloy components and shapes.

Nickelocene is used as a catalyst and complexing agent, and nickel titanate is used as a pigment (Antonsen & Meshri, 2005).

No information was available to the Working Group on the use of nickel selenides or potassium nickelocyanate.

1.4 Environmental occurrence

Nickel and its compounds are naturally present in the earth's crust, and are emitted to the atmosphere via natural sources (such as windblown dust, volcanic eruptions, vegetation forest fires, and meteoric dust) as well as from anthropogenic activities (e.g. mining, smelting, refining, manufacture of stainless steel and other nickel-containing alloys, fossil fuel combustion, and waste incineration). Estimates for the emission of nickel into the atmosphere from natural sources range from 8.5 million kg/year in the 1980s to 30 million kg/year in the early 1990s (ATSDR, 2005). The general population is exposed to low levels of nickel in ambient air, water, food, and through tobacco consumption.

1.4.1 Natural occurrence

Nickel is widely distributed in nature and is found in animals, plants, and soil (EVM, 2002). It is the 24th most abundant element, forming about 0.008% of the earth's crust (0.01% in igneous rocks). The concentration of nickel in soil is approximately 79 ppm, with a range of 4–80 ppm (EVM, 2002; ATSDR, 2005).

1.4.2 Air

Nickel is emitted to the atmosphere from both natural and anthropogenic sources. It has been estimated that approximately 30000 tonnes of nickel may be emitted per year to the atmosphere from natural sources. The anthropogenic emission rate is estimated to be between 1.4–1.8 times higher than the natural emission rate.

The two main natural sources are volcanoes and windblown dust from rocks and soil, estimated to respectively contribute 14000 tonnes/year and 11000 tonnes/year (NTP, 2000; Barbante *et al.*, 2002). Other relatively minor sources include: wild forest fires (2300 tonnes/year), sea salt spray (1300 tonnes/year), continental particulates (510 tonnes/year), marine (120 tonnes/year), and continental volatiles (100 tonnes/year) (Barbante *et al.*, 2002).

Anthropogenic activities release nickel to the atmosphere, mainly in the form of aerosols (ATSDR, 2005). Fossil fuel combustion is reported to be the major contributor of atmospheric nickel in Europe and the world, accounting for 62% of anthropogenic emissions in the 1980s (Barbante *et al.*, 2002; ATSDR, 2005). In 1999, an estimated 570000 tons of nickel were released from the combustion of fossil fuels worldwide (Rydh & Svärd, 2003). Of this, 326 tons were released from electric utilities (Leikauf, 2002). Of the other anthropogenic sources, nickel metal and refining accounted for 17% of total emissions, municipal incineration 12%, steel production 3%, other nickel-containing alloy production 2%, and coal combustion 2% (ATSDR, 2005).

Atmospheric nickel concentrations are higher in rural and urban air (concentration range: 5–35 ng/m^3) than in remote areas (concentration range: 1–3 ng/m^3) (WHO, 2007).

1.4.3 Water

Particulate nickel enters the aquatic environment from a variety of natural and anthropogenic sources. Natural sources include the weathering and dissolution of nickel-containing rocks and soil, disturbed soil, and atmospheric deposition. Anthropogenic sources include: industrial processes (e.g. mining and smelting operations), industrial waste water and effluent (e.g. tailings piles run-off), domestic waste water, and landfill leachate (NTP, 2000; ATSDR, 2005; WHO, 2007). Several factors influence the concentration of nickel in groundwater and surface water including: soil use, pH, and depth of sampling (WHO, 2007). Most nickel compounds are relatively water soluble at low pH (i.e. pH < 6.5). As a result, acid rain tends to increase the mobility of nickel in soil, which, in turn, has a corresponding impact on nickel concentrations in groundwater (NTP, 2000; WHO, 2007).

Based on measurement data from the 1980s, the following average nickel concentrations have been reported for groundwater, seawater and surface water, respectively: <20 µg/L, 0.1–0.5 µg/L, and 15–20 µg/L (NTP, 2000; ATSDR, 2005). Nickel concentrations as high as 980 µg/L have been measured in groundwater with pH < 6.2 (WHO, 2007). Levels of dissolved nickel ranging from < 1–87 µg/L have been reported in urban storm run-off water samples (ATSDR, 2005).

Nickel concentrations in the range of 6–700 pg/g have been measured in high-altitude snow and ice near the summit of Mont Blanc on the French-Italian border. Seasonal variations were observed, with higher concentrations in the summer layers than in the winter layers.

Nickel levels appeared to be more associated with anthropogenic inputs (e.g. oil combustion from power generation, automobile and truck traffic) than with natural sources, such as rock and soil dust (Barbante *et al.*, 2002).

1.4.4 Soil and sediments

Natural and anthropogenic sources (e.g. mining and smelting, coal fly ash, bottom ash, metal manufacturing waste, commercial waste, atmospheric fall-out and deposition, urban refuse, and sewage sludge) contribute to the levels of nickel found in soil and sediments (NTP, 2000; ATSDR, 2005). Of the nickel emitted to the environment, the largest releases are to the soil. In 2002, estimated releases of nickel and nickel compounds from manufacturing and processing facilities (required to report to the US Toxic Release Inventory Program) were approximately 5530 and 14800 metric tonnes, respectively—accounting for 82% and 87% of estimated total nickel releases to the environment (ATSDR, 2005).

In a study of urban soil quality, a harmonized sampling regime was used to compare concentrations of nickel in six European cities differing markedly in their climate and industrial history. The sites were as far as possible from current point sources of pollution, such as industrial emissions, but all were bordered by major roads, and are thus likely to have been affected by vehicle emissions. To assess the vertical distribution of soil parameters, two depths were sampled at each point: a surface sample at 0–10 cm and a subsurface sample at 10–20 cm. The surface sample mean nickel concentration was in the range of 11–207 mg /kg, and the corresponding mean concentration in the subsurface sample, 10–210 mg/kg (Madrid *et al.*, 2006).

1.5 Human exposure

1.5.1 Exposure of the general population

Ingestion of nickel in food, and to a lesser degree in drinking-water, is the primary route of exposure for the non-smoking general population. Exposure may also occur via inhalation of ambient air and percutaneous absorption (NTP, 2000; ATSDR, 2005; WHO, 2007). The daily intake of nickel from food and beverages varies by foodstuff, by country, by age, and by gender (EVM, 2002; ATSDR, 2005). Data from a study in the USA give estimates of daily dietary intakes in the range of 101–162 µg/day for adults, 136–140 µg/day for males, and 107–109 µg/day for females. Estimates for pregnant and lactating women are higher with average daily intakes of 121 µg/day and 162 µg/day, respectively (ATSDR, 2005). Based on the concordance between different studies of dietary intake, diet is reported to contribute less than 0.2 mg/day (WHO, 2007).

Inhalation of nickel from ambient air is generally a minor route of exposure for the general population. The following daily intakes of nickel have been estimated: less than 0.05 µg/day in the USA; 0.42 µg/day (mean ambient concentration) and 15 µg/day (highest ambient concentration) in the Sudbury basin region in Ontario, Canada; and, 122 µg/day (based on the highest ambient reported nickel concentration) in the Copper Cliff region of Ontario, Canada. These estimates are based on a breathing rate of 20 m^3/day, and nickel concentrations of 2.2 ng/m^3, 21 ng/m^3, 732 ng/m^3, and 6100 ng/m^3, respectively (ATSDR, 2005).

1.5.2 Occupational exposure

Nickel, in the form of various alloys and compounds, has been in widespread commercial use for over 100 years. Several million workers worldwide are exposed to airborne fumes, dusts and mists containing nickel and its compounds. Exposures by inhalation, ingestion or skin

contact occur in nickel-producing industries (e.g. mining, milling, smelting, and refining), as well as in nickel-using industries and operations (e.g. alloy and stainless steel manufacture; electroplating and electrowinning; welding, grinding and cutting). Insoluble nickel is the predominant exposure in nickel-producing industries, whereas soluble nickel is the predominant exposure in the nickel-using industries. Occupational exposure results in elevated levels of nickel in blood, urine and body tissues, with inhalation as the main route of uptake (IARC, 1990; NTP, 2000).

Estimates of the number of workers potentially exposed to nickel and nickel compounds have been developed by the National Institute of Occupational Safety and Health (NIOSH) in the USA and by CAREX (CARcinogen EXposure) in Europe. Based on the National Occupation Exposure Survey (NOES), conducted during 1981–1983, NIOSH estimated that 507681 workers, including 19673 female workers, were potentially exposed to 'Ni, Nickel-MF Unknown' (agent code: 50420) in the workplace (NIOSH, 1990). The following six industries accounted for nearly 60% of exposed workers: 'fabricated metal products' (n = 69984), 'special trade contractors' (n = 55178), 'machinery, except electrical' (n = 55064), 'transportation equipment' (n = 44838), 'primary metal industries' (n = 39467), and 'auto repair, services, and garages' (n = 27686). Based on occupational exposure to known and suspected carcinogens collected during 1990–1993, the CAREX database estimates that 547396 workers were exposed to nickel and nickel compounds in the European Union. Over 83% of these workers were employed in the 'manufacture of fabricated metal products, except machinery and equipment' (n = 195597), 'manufacture of machinery, except electrical' (n = 122985), 'manufacture of transport equipment' (n = 64720), 'non-ferrous base metal industries' (n = 32168), 'iron and steel basic industries' (n = 26504), and 'metal ore mining' (n = 16459). CAREX Canada (2011) estimates that approximately 50000 Canadians are exposed to nickel in the workplace (95% male). Exposed industries include: commercial/industrial machinery and equipment repair/maintenance; architectural, structural metals manufacturing; specialty trade contractors; boiler, tank and shipping container manufacturing; metal ore mining; motor vehicle parts manufacturing; machine shops, turned product, screw, nut and bolt manufacturing; coating, engraving, heat treating and allied activities; iron/steel mills and ferro-alloy manufacturing; non-ferrous metal production and processing.

Historically, metallic nickel exposures tended to be higher in nickel-producing industries than in the nickel-using industries, with estimates of historical mean levels of exposure to inhalable metallic nickel in the range of 0.01–6.0 mg/m^3 and 0.05–0.3 mg /m^3, respectively. However, data from the EU suggest that occasional higher exposures to inhalable metallic nickel may be present in certain industry sectors (Sivulka, 2005).

Data on early occupational exposures to nickel and nickel compounds were summarized in the previous *IARC Monograph* (IARC, 1990). Data from studies and reviews on nickel exposure published since the previous *IARC Monograph* are summarized below for both the nickel-producing and the nickel-using industries.

(a) *Studies of nickel-producing industries*

Ulrich *et al.* (1991) collected data on several indicators of nickel exposure (stationary and personal air sampling; urinary nickel excretion) among electrolytic nickel production workers in the Czech Republic (formerly, Czechoslovakia). Air samples (n = 52) were collected on membrane filters and analysed by electrothermal atomic absorption spectrometry. Urine samples (n = 140) were collected during the last 4 hours of workers' shifts, and the results were corrected to a standard density of 1.024. In a matched-pair analysis of air and urine samples collected from 18 electrolysis workers, the correlation coefficient

was 0.562; the mean concentration of nickel in urine was 53.3 μg/L (range, 1.73–98.55 μg/L), and the mean concentration in air was 0.187 mg/m^3 (range, 0.002–0.481 mg/m^3).

In a study conducted at a Finnish electrolytic nickel refinery, Kiilunen *et al.* (1997) collected data on nickel concentrations in air, blood, and urine. Stationary samples (n = 141) were collected from 50 locations in the refinery, including those areas where breathing zone samples were taken. Personal (i.e. 8-hour breathing zone) samples were collected over 4 successive work days (n = 157), from the shoulders when no respiratory protection was worn, inside the mask when protective equipment was worn, and inside the mask hanging on the shoulder of the worker when the mask was taken off. Historical occupational hygiene measurements were examined to assess past exposure. Spot urine samples (n = 154) were collected, pre- and post-shift, over 4 successive work days and 1 free day thereafter. Blood samples (n = 64) were collected at the beginning of the study and at the end of the last work shift. A total of 34 workers (of 100) volunteered to participate in the study. Urinary nickel results in the workers were compared with two non-exposed control groups (30 office workers from the refinery and 32 unexposed persons from the Helsinki area). For the stationary samples, nickel concentrations were reported by location as water-soluble nickel, acid-soluble nickel and total nickel (all in μg/m^3). Geometric mean nickel concentrations ranged from: 7.4 μg/m^3 ('other sites') to 451 μg/m^3 (in 'tank house 3') for water-soluble nickel; 0.5 μg/m^3 ('other sites') to 4.6 μg/m^3 ('solution purification') for acid-soluble nickel; and, 7.6 μg/m^3 ('other sites') to 452 μg/m^3 (in 'tank house 3'). For the breathing zone samples, the range of geometric mean nickel concentrations was 0.2–3.2 μg/m^3 (inside the mask) and 0.6–63.2 μg/m^3 (no mask). Based on a review of historical stationary sampling data, average nickel concentrations varied in the range of 230–800 μg/m^3 over the period 1966–88. Lower concentrations (112–484 μg/m^3) were observed in the early 1990s. Geometric mean after-shift urinary concentrations of nickel were in the range of 0.1–0.8 μmol/L (mask in use) and 0.5–1.7 μmol/L (no mask in use). Urinary nickel concentrations were still elevated after 2- and 4-week vacations. No consistent correlations between airborne nickel concentrations and nickel concentrations in the blood or urine were observed.

Thomassen *et al.* (2004) measured the exposure of 135 copper refinery workers (45 females, 90 males) to copper, nickel and other trace elements at a nickel refinery complex in Monchegorsk, the Russian Federation. Full-shift breathing zone samples were collected for workers in the pyrometallurgical process (n = 138) and in the electrorefining process (n = 123) areas. Workers wore personal samplers for two to four full shifts. IOM samplers were used to assess the inhalable aerosol fraction, and Respicon samplers (3-stage virtual impactors) were used to separate the inhalable fraction into respirable, tracheobronchal, and extrathoracic aerosol fractions. The geometric mean inhalable nickel concentration was in the range of 0.024–0.14 mg/m^3 for samples taken in the pyrometallurgical areas, and 0.018–0.060 mg/m^3 for samples taken in the electrorefining areas (data presented as the sum of the inhalable water-soluble and water-insoluble subfractions). For the inhalable aerosol nickel concentrations observed in the pyrometallurgical process steps, the water-insoluble subfraction contained higher levels than the water-soluble fraction, with geometric means of 59 μg/m^3 and 14 μg/m^3, respectively. In the electrorefining process area, the nickel concentrations in the inhalable subfractions were 14 μg/m^3 (water-soluble) and 10 μg/m^3 (water-insoluble).

Air monitoring was conducted in three areas of a nickel base metal refinery in South Africa (the ball mill area, the copper winning area, and the nickel handling area). Personal breathing zone samples (n = 30) were collected in all areas of the

plant, and were analysed gravimetrically and by inductively coupled plasma mass spectroscopy. The mean time-weighted average concentrations for soluble, insoluble and total nickel dust, respectively, were 44, 51, and 95 μg/m³ in the ball mill area; 395, 400, and 795 μg/m³ in the nickel handling area; and 46, 17, and 63 μg/m³ in the copper winning area (Harmse & Engelbrecht, 2007).

Airborne dust concentrations, nickel concentrations, nickel speciation, and aerosol particle size distributions in two large-scale nickel production facilities were assessed by collecting a total of 46 inhalable samples (30 personal, 16 area), and 28 cascade impactor samples (18 personal, 10 area). Samples were collected using IOM and Marple cascade impactor sampling heads, and analysed gravimetrically. At the first site, inhalable concentrations were in the range of 0.5–9.1 mg/m³ for the personal samples, and 0.2–5.7 mg/m³ for the area samples (median concentrations, 0.7 mg/m³ and 0.4 mg/m³, respectively). Total nickel levels in the personal samples were in the range of 1.8–814.9 μg/m³, and 19.8–2481.6 μg/m³ in the area samples (median concentrations, 24.6 μg/m³ and 92.0 μg/m³, respectively). At the second site, airborne concentrations of inhalable dust were in the range of 1.2–25.2 mg/m³ for the personal samples, and 1.5–14.3 mg/m³ (median concentrations, 3.8 mg/m³ and 2.9 mg/m³, respectively) for the area samples. Total nickel levels were in the range of 36.6–203.4 μg/m³ in the area samples, and 0.2–170.7 μg/m³ in the personal samples (median concentrations, 91.3 and 15.2 μg/m³, respectively) (Creely & Aitken, 2008).

(b) Studies of nickel-using industries

Bavazzano *et al.* (1994) collected air, face, hand, and spot urine samples from 41 male workers in electroplating operations in 25 small factories in the province of Florence, Italy, and compared them to samples collected from non-exposed male subjects (face and hand samples: n = 15 subjects aged 15–60 years old; urine samples: n = 60 subjects aged 22–63 years old). For the airborne nickel measurements, personal exposure were in the range of 0.10–42 μg/m³ (median concentration, 2.3 μg/m³). The median nickel levels in the urine, on the hands, and on the face were, respectively, 4.2 μg/L (range, 0.7–50 μg/L), 39 μg (range, 1.9–547 μg), and 9.0 μg (range, 1.0–86 μg). Median hand, face, and urine nickel levels for the control subjects were, respectively, 0.8 μg (range, 0.0–5.3 μg; n = 15), 0.30 μg (range, 0.0–2.4; n = 15), and 0.7 μg (range, 0.1–2.5 μg; n = 60).

In an occupational hygiene survey of 38 nickel electroplating shops in Finland, exposure to nickel was assessed by questionnaire (n = 163), urine samples (phase 1: n = 145; phase 2: n = 104), bulk samples (n = 30), and air measurements in three representative shops (one clean, one intermediate, one dirty) on 1 day during which urine samples were also being collected. Full-shift breathing zone samples were collected from inside and outside a respirator with filters. In the first phase of the study, average urinary nickel concentration was 0.16 μmol/L (range, 0.0–5.0 μmol/L; n = 145). The range of mean values for different workplaces was 0.01–0.89 μmol/L, and for the median values, 0.02–0.05 μmol/L. For the 97 workers followed in the second phase, urinary nickel concentrations were observed to fluctuate with exposure, with mean nickel concentrations in the range of 0.10–0.11 μmol/L for the morning specimens, and 0.12–0.16 μmol/L for the afternoon specimens. Personal breathing zone nickel concentrations were as follows: 0.5 μg/m³ (hanger worker in the 'clean shop'), 0.7 μg/m³ (worker responsible for maintenance of nickel bath in the 'clean' shop), and in the range of 5.6–78.3 μg/m³ for workers (n = 6) in the 'dirty' shop. In the area samples, nickel concentrations were 26 μg/m³ (near the nickel bath in the 'clean' shop), 11.9–17.8 μg/m³ (in the hanging area of the 'dirty' shop), and 73.3 μg/m³ (beside the nickel bath in the 'dirty' shop) (Kiilunen *et al.*, 1997).

Kiilunen (1997) analysed data from the biomonitoring registry and the occupational hygiene service registry of the Finnish Institute of Occupational Health to examine trends in nickel exposure during 1980–89. A total of 1795 urinary nickel samples (for which it was possible to identify job titles) were examined, along with 260 nickel measurements from the breathing zone of workers for whom job titles were available. Across all job titles, the ranges of mean urinary nickel concentrations, by time period, were as follows: 0.05–0.52 µmol/L for 1980–82, 0.14–0.51 µmol/L for 1983–85, and 0.17–0.87 µmol/L for 1986–89. The two largest occupational groups sampled were platers (n = 503), and welders (n = 463). Mean urinary concentrations for platers, by time period, were 0.35 µmol/L for 1980–82 (range, 0.01–2.95), 0.30 µmol/L for 1983–85 (range, 0.01–2.10), and 0.38 µmol/L for 1986–89 (range, 0.03–2.37). Mean urinary concentrations for welders, by time period, were 0.22 µmol/L for 1980–82 (range, 0.03–1.58), 0.17 µmol/L for 1983–85 (range, 0.03–0.65), and 0.21 µmol/L for 1986–89 (range, 0.01–1.58). Analysis of the breathing zone measurements revealed that 22.1% of all measurements in 1980–82 had exceeded the occupational exposure limit (OEL) of 0.1 mg/m^3. Similar results were seen for the 1983–85 period (24.8%), rising to 30.7% for the 1986–89 period. Job titles with mean values over the OEL in 1983–85 included: grinders (mean, 0.76 mg/m^3, n = 29), one metal worker (0.12 mg/m^3), powder cutters (mean, 0.34 mg/m^3, n = 31), one spray painter (0.20 mg/m^3), and welders (0.17 mg/m^3, n = 72). Mean levels exceeded the OEL in the following four occupational groups during 1986–89: carbon arc chisellers (mean, 0.6 mg/m^3, n = 2), grinders (mean, 0.28 mg/m^3, n = 19), one warm handler (0.18 mg/m^3), and burn cutters (mean, 0.14 mg/m^3, n = 2).

The association between occupational exposure to airborne nickel and nickel absorption was examined by collecting personal breathing zone samples and urine samples from 10 workers at a galvanizing plant in Brazil that uses nickel sulfate. Spot urine samples were collected pre- and post-shift from the nickel-exposed workers over 5 consecutive days, and from 10 non-nickel exposed workers employed at a zinc plant over 3 consecutive days (n = 97 and 55, respectively). Both groups completed a questionnaire on occupational history, health and lifestyle factors; exposed workers also underwent a medical examination. Personal breathing zone samples (first 4 hours of shift) were collected using NIOSH protocols. Geometric mean airborne nickel levels were in the range of 2.8–116.7 µg/m^3, and the urine levels, from samples taken post-shift, were in the range of 4.5–43.2 µg/g creatinine (mean, 14.7 µg/g creatinine) (Oliveira *et al.*, 2000).

Sorahan (2004) examined data on mean (unadjusted) levels of exposure to inhalable nickel at a nickel alloy plant during 1975–2001 in Hereford, the United Kingdom. Data were reported for two time periods: 1975–80 and 1997–2001. Mean nickel levels (unadjusted) for the earlier period were as follows: 0.84 mg/m^3 in the melting, fettling, and pickling areas; 0.53 mg/m^3 in the extrusion and forge, hot strip and rolling, engineering, and melting stores areas; 0.55 mg/m^3 in the machining, hot rolling, Nimonic finishing, and craft apprentice areas; 0.40 mg/m^3 in the roll turning and grinding, cold rolling, cold drawing, wire drawing, and inspection areas; and 0.04 mg/m^3 in the process stock handling, distribution and warehouse areas. The corresponding mean nickel levels (unadjusted) for the latter period were: 0.37 mg/m^3, 0.45 mg/m^3, 0.31 mg/m^3, 0.30 mg/m^3, and 0.29 mg/m^3, respectively.

Eight-hour TWA (8-h TWA) exposures calculated for the period 1997–2001 were 0.33 mg/m^3, 0.31 mg/m^3, 0.16 mg/m^3, 0.16 mg/m^3, and 0.27 mg/m^3, respectively.

Sorahan & Williams (2005) assessed the mortality of workers at a nickel carbonyl refinery in Clydach, the United Kingdom to determine whether occupational exposure to nickel resulted in increased risks of nasal cancer and lung cancer.

Using personal sampling data collected in the 1980s and 1990s, 8-h TWA exposure to total inhalable nickel was calculated, and assigned to six categories of work, based on the predominant species of nickel exposure. The six categories of work were: feed handling and nickel extraction, including kilns (oxide/metallic); pellet and powder production, and shipping (metallic); nickel salts and derivatives, and effluent (metallic/soluble); wet treatment and related processes (metallic/subsulfide/soluble); gas plant (non-nickel); and engineering and site-wide activities that could include any of the preceding work areas. Mean levels of total inhalable nickel dust were in the range of 0.04–0.57 mg/m^3 in the 1980s (n = 1781), and 0.04–0.37 mg/m^3 in the 1990s (n = 1709).

Stridsklev *et al.* (2007) examined the relationship between the concentration of airborne nickel in the occupational environment of grinders (n = 9) grinding stainless steel in Norway and the concentration of nickel in their urine and blood. Grinders either worked in a well ventilated hall of a shipyard or in a small non-ventilated workshop. The sampling protocol was as follows: full-shift personal samples were collected in the breathing zone of grinders over the course of 1 work week; urine samples were collected three times daily for 1 week (first void in the morning, pre- and post-shift); and blood samples were drawn twice daily for 3 days in 1 week (pre- and post-shift). Blood and urine samples were also collected on the Monday morning after a 3-week vacation in the workshop. Grinders also completed a questionnaire to collect information on work history, use of personal protective equipment, and smoking habits. Mean levels of airborne nickel were 18.9 µg/m^3 (range, 1.8–88.6 µg/m^3) in the shipyard, and 249.8 µg/m^3 (range, 79.5–653.6 µg/m^3) in the workshop. Mean blood nickel levels for grinders were 0.87 µg/L (range, < 0.8–2.4 µg/L) in whole blood, and 1.0 µg/L (range, < 0.4–4.1 µg/L) in plasma. Mean urinary nickel levels for grinders were 3.79 µg/g creatinine (range, 0.68–10.6 µg/g creatinine), 3.39 µg/g creatinine (range, 0.25–11.1 µg/g creatinine), and 4.56 µg/g creatinine (range, < 0.53–11.5 µg/g creatinine), from the first void, pre- and post-shift samples, respectively. With the exception of stainless steel welders welding the MIG/MAG-method [Metal Inert Gas-Metal Active Gas], mean urinary nickel levels were higher in grinders than in welders. Mean urinary nickel levels in MIG/MAG welders were 5.9 µg/g creatinine (range, < 0.24–20.5 µg/g creatinine), 3.8 µg/g creatinine (range, 0.33–11.4 µg/g creatinine), and 4.6 µg/g creatinine (range, < 0.25–18.4 µg/g creatinine) from the first void, pre-, and post-shift samples, respectively.

Sivulka & Seilkop (2009) reconstructed historical exposures to nickel oxide and metallic nickel in the US nickel alloy industry from personal and area measurements collected at 45 plants since the 1940s (n = 6986 measurements). Of the measurements included in the database, 96% were personal breathing zone samples, and 4% were stationary area samples. The data provided evidence of a strongly decreasing gradient of airborne total nickel levels from the 1940s to the present.

1.5.3 Dietary exposure

Nickel has been measured in a variety of foodstuffs as "total nickel." Average concentrations are in the range of 0.01–0.1 mg/kg, but can be as high as 8–12 mg/kg in certain foods (EVM, 2002; WHO, 2007). Factors influencing the concentration of nickel in food include the type of food (e.g. grains, vegetables, fruits versus seafood, mother's milk versus cow's milk), growing conditions (i.e. higher concentrations have been observed in food grown in areas of high environmental or soil contamination), and food preparation techniques (e.g. nickel content of cooking utensils, although the evidence for leaching from stainless steel cookware is somewhat mixed) (EVM, 2002; WHO, 2007).

The highest mean concentrations of nickel have been measured in beans, seeds, nuts and grains (e.g. cocoa beans, 9.8 µg/g; soyabeans, 5.2 µg/g; soya products, 5.1 µg/g; walnuts, 3.6 µg/g; peanuts, 2.8 µg/g; oats, 2.3 µg/g; buckwheat, 2.0 µg/g; and oatmeal, 1.8 µg/g). Although nickel concentrations vary by type of foodstuff, average levels are generally within the range of 0.01–0.1 µg/g. Reported ranges for some common food categories are: grains, vegetables and fruits, 0.02–2.7 µg/g; meats, 0.06–0.4 µg/g; seafood, 0.02–20 µg/g; and dairy, < 100 µg/L (EVM, 2002). This variability in nickel content makes it difficult to estimate the average daily dietary intake of nickel (EVM, 2002).

1.5.4 Biomarkers of exposure

Biomarker levels are influenced by the chemical and physical properties of the nickel compound studied, and by the time of sampling. It should be noted that the nickel compounds, the timing of collection of biological samples (normally at the end of a shift), and the analytical methods used differ from study to study, and elevated levels of nickel in biological fluids and tissue samples are mentioned only as indications of uptake of nickel, and may not correlate directly to exposure levels (IARC, 1990).

Atomic absorption spectrometry (AAS) and inductively coupled plasma atomic emission spectroscopy (ICP-AES) are the most common analytical methods used to determine "total nickel" concentrations in biological materials (such as blood, tissues, urine, and faeces). Nickel content can also be measured in other tissues, such as nails and hair, although specific procedures for dissolving the sample must be followed (ATSDR, 2005). The presence of calcium, sodium or potassium interferes with the quantification of nickel in biological samples, and specific techniques (e.g. isotope dilution) must be used to validate nickel measurements (ATSDR, 2005). Serum and urine samples are the most useful biomarkers of recent exposure, reflecting the amount of nickel absorbed in the previous 24–48 hours (NTP, 2000).

Minoia *et al.* (1990) used atomic absorption spectroscopy and neutron activation analysis to determine trace element concentrations of nickel in urine, blood, and serum collected from non-exposed healthy subjects (n = 1237; 635 males, 602 females) from the Lombardy region of northern Italy. The mean nickel level in urine samples (n = 878) was 0.9 µg/L (range, 0.1–3.9 µg/L); in blood samples (n = 36), 2.3 µg/L (range, 0.6–3.8 µg/L); and in serum samples (n = 385), 1.2 µg/L (range, 0.24–3.7 µg/L).

In a Norwegian-Russian population-based health study, human nickel exposure was investigated in the adult population living near a nickel refinery on both sides of the Norwegian-Russian border during 1994–95. Urine samples were collected from inhabitants, aged 18–69 years, of Nikel, Zapolyarny, and Sor-Varanger and also from individuals living more remotely from the Kola Peninsula nickel-producing centres (in the Russian cities of Apatity and Umba, and the Norwegian city of Tromso). A total of 2233 urine specimens were collected and analysed for nickel using electrothermal atomic absorption spectrometry. The highest urinary nickel concentrations were observed in residents of Nikel (median, 3.4 µg/L; mean, 4.9 µg/L; range, 0.3–61.9 µg/L), followed by Umba (median, 2.7 µg/L; mean, 4.0 µg/L; range, 1.0–17.0 µg/L), Zapolyarny (median, 2.0 µg/L; mean, 2.8 µg/L; range, 0.3–24.2 µg/L), Apatity (median, 1.9 µg/L; mean, 2.6 µg/L; range, 0.3–17.0 µg/L), Tromso (median, 1.2 µg/L; mean, 1.4 µg/L; range, 0.3–6.0 µg/L), and Sor-Varanger (median, 0.6 µg/L; mean, 0.9 µg/L; range, 0.3–11.0 g/L). The Russian participants all had a higher urinary nickel average than those from Norway, regardless of geographic location (Smith-Sivertsen *et al.*, 1998).

Ohashi *et al.* (2006) determined reference values for nickel in urine among women of the general population of 11 prefectures in Japan.

A total of approximately 13000 urine samples were collected in 2000–05 from 1000 adult women aged 20–81 years who had no occupational exposure to nickel. Nickel in urine was analysed by graphite furnace atomic absorption spectrometry. The observed geometric mean concentration for nickel was 2.1 µg/L (range, < 0.2–57 µg/L). After correction for creatinine, the geometric mean concentration was reported as 1.8 µg/L (maximum, 144 µg/L).

1.5.5 Other sources of exposure

Nickel, chromium, and cobalt are common causes of allergic contact dermatitis. In the early 1990s it was recommended that household and other consumer products should not contain more than 5 ppm of each of nickel, chromium, or cobalt, and that, for an even greater degree of protection, the ultimate target level should be 1 ppm. In a recent survey, selected consumer products had the following nickel levels (ppm): hand-wash powders, 0.9; heavy duty powders, 0.5; laundry tablets, 0.5; liquid/powder cleaners, 0.4; heavy duty liquids, 0.1; machine/hand-wash liquids, 0.1; hand-wash liquids, 0.1, fine wash liquids, 0.1; and dishwashing liquids, 0.1 (Basketter *et al.*, 2003).

Potential iatrogenic sources of exposure to nickel are dialysis treatment, leaching of nickel from nickel-containing alloys used as prostheses and implants, and contaminated intravenous medications (Sunderman, 1984).

2. Cancer in Humans

The previous *IARC Monograph* was based upon evidence of elevated risk of lung and nasal cancers observed among workers involved in a variety of nickel sulfide ore smelting and nickel refining processes that included high-temperature processing of nickel matte, nickel–copper matte, electrolytic refining, and Mond process refining. The exposures included metallic nickel, nickel oxides, nickel subsulfide, soluble nickel compounds, and nickel carbonyl. These cohort studies were conducted mainly in Canada, Norway, Finland, and in the United Kingdom (IARC, 1990; ICNCM, 1990).

2.1 Cohort studies and nested case–control studies

Since the previous *IARC Monograph*, several studies have extended follow-up to some of the previous cohorts, and have provided additional cohort and nested case–control analyses related mostly to lung cancer risk, and taking into account potential confounding factors as well as mixed exposures to water-soluble and -insoluble nickel compounds. Among the most common occupations with exposure to nickel compounds are stainless steel welders, who are also exposed to chromium (VI) compounds, and other compounds. Although there have been some cohort studies of stainless steel welders, these are not recorded in the present *Monograph* because it is difficult to ascribe any excess risks in these cohorts to nickel compounds specifically. Key results of some of these cohort studies can be found in Table 2.1 of the *Monograph* on chromium (VI) in this volume.

Also, since the previous *IARC Monograph*, experimental evidence has become available that nickel metal dust can become solubilized and bioavailable after inhalation. Consequently, separately classifying nickel and nickel compounds was viewed by the Working Group as not warranted. A similar distinction has not been made for other metals, e.g. beryllium and cadmium, in other *IARC Monographs*. Accordingly, this review did not exclude studies that focused on metallic nickel, unless they, for other reasons, were considered uninformative.

2.1.1 Cancer of the lung

Studies were carried out in nickel smelters and refineries in Canada, Norway (Kristiansand), Finland, and the United Kingdom (Clydach). Because the refining processes differed in the plants, the exposure profiles to various nickel compounds were different across the cohorts. Nonetheless, increased risks for lung cancer were found in cohorts from all of these facilities (see Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-05-Table2.1.pdf).

High risks for lung cancers were observed among calcining workers in Canada, who were heavily exposed to both sulfidic and oxidic nickel (nickel sulfides and oxides). A high lung cancer rate was also seen among nickel plant cleaners in Clydach who were heavily exposed to these insoluble compounds, with little or no exposure to soluble nickel. The separate effects of oxides and sulfides could not be estimated, however, as high exposure was always either to both, or to oxides together with soluble nickel. Workers in Clydach calcining furnaces and nickel plant cleaners, exposed to high levels of metallic nickel, had high lung cancer risks (see Table 2.1 online). A substantial excess risk for lung cancer among hydrometallurgy workers in Norway was mainly attributed to their exposure to water-soluble nickel. Their estimated exposures to other types of nickel (metallic, sulfidic, and oxidic) were as much as an order of magnitude lower than those in several other areas of the refinery, including some where cancer risks were similar to those observed in hydrometallurgy. High risks for lung cancer were also observed among electrolysis workers at Kristiansand (Norway). These workers were exposed to high estimated levels of soluble nickel and to lower levels of other forms of nickel. Nickel sulfate and nickel chloride (after 1953) were the only or predominant soluble nickel species present in these areas.

An update of the Kristiansand cohort by Andersen *et al.* (1996) demonstrated a dose–response relationship between cumulative exposure to water-soluble nickel compounds and lung cancer ($P < 0.001$) when adjustment was made for age, smoking, and nickel oxide. The risk was increased 3-fold in the highest soluble nickel dose group. A lesser, but positive, effect was seen between cumulative exposure to nickel oxide and risk of lung cancer, also with adjustment for age, cigarette smoking, and exposure to water-soluble nickel (P for trend = 0.05, see Table 2.2).

Subsequent to the Andersen *et al.* (1996) study, an industrial hygiene study re-evaluated exposure among the Norwegian refinery workers based on new information related to nickel species and exposure levels (Grimsrud *et al.*, 2000). Grimsrud *et al.* (2003) updated the lung cancer incidence among the Norwegian nickel refinery workers (see Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-05-Table2.3.pdf). The strongest gradient for cumulative exposure and lung cancer was found in relation to water-soluble nickel adjusted for cigarette-smoking habits, which was known for 4728 (89%) of the cohort members. Regarding species of water-soluble nickel compounds, the risk from potential exposure to nickel chloride was similar to that for nickel sulfate. The nickel electrolysis process (using nickel sulfate) changed to a nickel-chloride-based process in 1953, and workers hired in 1953 or later had a similar lung cancer risk (standardized incidence ratio [SIR], 4.4; 95%CI: 1.8–9.1) as for those employed in the same area before 1953 when the nickel sulfate was used (SIR, 5.5; 95%CI: 3.0–9.2). Analyses by year of first employment indicated that those initially employed after 1978 continued to demonstrate a significantly elevated risk of lung cancer (SIR, 3.7; 95%CI: 1.2–8.7), suggesting continued exposure to nickel compounds.

Grimsrud *et al.* (2002) conducted a case–control study of lung cancer nested within the

Table 2.2 Relative risks of lung cancer by cumulative exposure to soluble nickel and nickel oxide, considering the two variables simultaneously by multivariate Poisson regression analysis[a]

Variable	Mean exposure (mg/m^3)	Cases	Relative risk	95%CI	Test for linear trend
Soluble nickel					$P < 0.001$
< 1	0.1	86	1.0	Referent	
1–4	2.3	36	1.2	0.8–1.9	
5–14	8.8	23	1.6	1.0–2.8	
≥ 15	28.9	55	3.1	2.1–4.8	
Nickel oxide					$P = 0.05$
< 1	0.4	53	1.0	Referent	
1–4	2.5	49	1.0	0.6–1.5	
5–14	8.3	53	1.6	1.0–2.5	
≥ 15	44.3	45	1.5	1.0–2.2	

[a] Workers with unknown smoking habits were excluded (three cases of lung cancer).
Adjusted for smoking habits and age.
From Andersen *et al.* (1996)

cohort of Norwegian nickel refinery workers (see Table 2.3 online). Exposure groups were determined based on quintiles of the exposure variables in the controls. Analyses by cumulative exposure adjusted for cigarette smoking indicated that odds ratios for lung cancer in the highest cumulative exposure category of water-soluble nickel, sulfidic nickel, metallic nickel, and oxidic nickel were 3.8 (95%CI: 1.6–9.0), 2.8 (95%CI: 1.1–6.7), 2.4 (95%CI: 1.1–5.3), and 2.2 (95%CI: 0.9–5.4), respectively. The trend for cumulative exposure and lung cancer was significant for water-soluble nickel compounds only ($P = 0.002$). There was, however, a high degree of correlation with exposure to nickel and nickel compounds as a whole, making evaluation of the independent effect of individual compounds difficult. Nonetheless, when data were further adjusted for exposure to water-soluble compounds, there were no significant trends in the odds ratios by cumulative exposure to sulfidic, oxidic, or metallic nickel. The odds ratios related to the highest cumulative exposure group for each of these compounds were 1.2 (95%CI: 0.5–3.3), 0.9 (95%CI: 0.4–2.5), and 0.9 (95%CI: 0.3–2.4), respectively (see Table 2.4). In further analyses, with adjustment for cigarette smoking, arsenic, asbestos, sulfuric acid mist, cobalt and occupational carcinogenic exposures outside the refinery, the strong association between lung cancer and water-soluble nickel remained (Grimsrud *et al.*, 2005).

Anttila *et al.* (1998) updated an earlier cohort study of Finnish nickel refinery and copper/nickel smelter workers (Karjalainen *et al.*, 1992). Among refinery workers employed after 1945, who were exposed primarily to nickel sulfate, an excess of lung cancer was observed in the overall cohort (SIR, 2.61; 95%CI: 0.96–5.67), and the lung cancer risk increased with > 20 years of latency (SIR, 3.38; 95%CI: 1.24–7.36, based on six cases). Among smelter workers, lung cancer was also elevated in the overall cohort (SIR, 1.39; 95%CI: 0.78–2.28), and, similarly, a significant increase in lung cancer risk with > 20 years of latency was observed (SIR, 2.00; 95%CI: 1.07–3.42).

There have been three subsequent reports that provide additional information on refinery workers in Wales (the United Kingdom) exposed to nickel carbonyl and other nickel compounds.

Easton *et al.* (1992) carried out an updated analysis of Welsh nickel refinery workers to determine which nickel compounds were responsible for lung cancer among the 2524 workers employed

Table 2.4 Adjusted[a] odds ratios for lung cancer by exposure to sulfidic, oxidic or metallic nickel in a nested case–control study of Norwegian nickel refinery workers observed during 1952–95

Cumulative exposure to nickel[b]	Odds ratio	95% CI
Sulfidic nickel		
Unexposed	1.0	
Low	1.5	0.6–3.9
Low-medium	2.2	0.9–5.5
Medium	1.8	0.7–4.5
Medium-high	1.3	0.5–3.3
High	1.2	0.5–3.3
Likehood ratio test: $P = 0.344$		
Oxidic nickel		
Unexposed	1.0	
Low	1.5	0.6–3.8
Low-medium	1.8	0.7–4.5
Medium	1.4	0.6–3.7
Medium-high	1.5	0.6–3.7
High	0.9	0.4–2.5
Likehood ratio test: $P = 0.406$		
Metallic nickel		
Unexposed	1.0	
Low	1.2	0.5–2.9
Low-medium	1.0	0.5–2.4
Medium	1.0	0.4–2.3
Medium-high	1.0	0.4–2.4
High	0.9	0.3–2.4
Likehood ratio test: $P = 0.972$		

[a] Data were adjusted for smoking habits in five categories (never smoker, former smoker, or current smoker of 1–10, 11–20, or > 20 g/day), and for exposure to water-soluble nickel as a continuous variable with natural log-transformed cumulative exposure values (ln[(cumulative exposure) + 1]).

[b] Categories were generated according to quartiles among exposed control. In each of the three analyses, data were unadjusted for the other two insoluble forms of nickel.

From Grimsrud *et al.* (2002)

for > 5 years before the end of 1969, and followed during 1931–85. The model was based on exposures occurring before 1935, and was adjusted for age at first exposure, duration of exposure, and time since first exposure. For lung cancer, the best fitting model suggested risks for soluble and metallic nickel exposures, and much less (if any) risk for nickel oxide or sulfides. Sorahan & Williams (2005) followed during 1958–2000 a group of 812 workers from the cohort of Welsh nickel refinery workers who were hired between 1953–92, and who had achieved > 5 years of employment. The overall lung cancer SMR was 1.39 (95%CI: 0.92–2.01). For those with > 20 years since the start of employment, lung cancer risk was significantly elevated [SMR, 1.65; 95%CI: 1.07–2.41], indicating an elevated risk of lung cancer among those hired since 1953.

Grimsrud & Peto (2006) combined data from the most recent updates of Welsh nickel refinery workers to assess lung cancer mortality risk by period of initial employment. For those first employed since 1930, an elevated risk was observed for lung cancer (SMR, 1.33; 95%CI: 1.03–1.72). [The Working Group noted that

exposures were dramatically reduced during the 1920s.]

Egedahl *et al.* (2001) updated the mortality data among employees at a hydrometallurgical nickel refinery and fertilizer complex in Fort Saskatchewan, Canada, who had worked for 12 continuous months during 1954–78. Among the 718 men exposed to nickel, the lung cancer SMR was 0.67 (95%CI: 0.24–1.46, based on six deaths). Significant decreases were observed for the 'all causes of death' category (SMR, 0.57; 95%CI: 0.43–0.74), and for the 'all cancer deaths' category (SMR, 0.47; 95%CI: 0.25–0.81). [The Working Group considered the study uninformative for the evaluation of cancer risks due to a substantial healthy worker effect which may have masked excess mortality that was associated with nickel exposure.]

Goldberg *et al.* (1994) conducted a 10-year incidence study and a nested case–control study of a cohort of nickel mining (silicate-oxide ores) and refinery workers in New Caledonia, South Pacific. They observed a significant decrease in the incidence of lung cancer, and this was also observed for other respiratory cancers The results of the case–control study did not show elevated risks for respiratory cancers in relation to low levels of exposure to soluble nickel, nickel sulfide, or metallic nickel. For all three nickel exposures separately, the odds ratios were 0.7.

[The Working Group noted that in most of these studies of lung cancer risk in smelters and refineries, there was exposure to metallic nickel together with exposure to the other forms of nickel (Sivulka, 2005). Only one of these studies involved an attempt to evaluate separately the effect of metallic nickel (Grimsrud *et al.*, 2002).]

Several additional studies of workers with potential exposure to metallic nickel were reviewed by the Working Group. Arena *et al.* (1998) evaluated mortality among workers exposed to "high nickel alloys" in the USA. A recent industrial hygiene analysis indicated that oxidic nickel comprised 85% of the total nickel exposure of these workers, with the rest being mostly metallic nickel (Sivulka & Seilkop, 2009). Compared to US national rates, lung cancer was significantly elevated among white men (SMR, 1.13; 95%CI: 1.05–1.21), among non-white men the SMR was 1.08 (95%CI: 0.85–1.34), and in women 1.33 (95%CI: 0.98–1.78). [The Working Group noted that the lung cancer SMR for the entire cohort combined was 1.13 (95%CI: 1.06–1.21) based on 955 observed deaths.] The authors also calculated SMRs based on local (SMSA) rates for the separate population subgroups. When calculated for the total cohort, the resulting SMR was [1.01; 95%CI: 0.95–1.08]. [The Working Group noted that it is difficult to interpret the use of local rates when the study population was derived from 13 separate areas located throughout the USA, but the use of rates from urban areas could have overestimated the expected number of deaths from lung cancer. The Working Group noted that the overall SMR for lung cancer in this study compared with the national population was statistically significant, and provides some evidence of an association between exposures in these plants and lung cancer. It appears that the primary exposure was to nickel oxide and thus, the study cannot be used to evaluate the specific carcinogenicity of metallic nickel. Analysis of lung cancer by duration of employment did not indicate a dose–response. The Working Group noted that duration of employment is a poor measure of exposure when exposures are known to have declined over time.]

There have also been a series of studies conducted in the French stainless steel industry that involved co-exposure to several known and potential human lung carcinogens, and the most detailed exposure assessment considered nickel and chromium combined (Moulin *et al.* 1990, 1993a, b, 1995, 2000).]

The only cohort of workers exposed to metallic nickel in the absence of other nickel compounds (Oak Ridge cohort) included only 814 workers, and provided little statistical power to evaluate

lung cancer risk (Godbold & Tompkins, 1979; Cragle *et al.*, 1984).

Sorahan (2004) updated the mortality rate among employees manufacturing nickel alloys at the plant in Hereford, the United Kingdom. The study showed a significant decrease for 'all causes of death' (SMR, 0.79), for 'all cancer deaths' (SMR, 0.81), and a non-significant decrease for lung cancer (SMR, 0.87; 95%CI: 0.67–1.11).

Pang *et al.* (1996) evaluated cancer risks among 284 men who were employed for at least 3 months during 1945–75 in a nickel-plating department, and followed through 1993. For lung cancer, the overall SMR was 1.08 (95%CI: 0.54–1.94). For those with > 20 years latency, eight lung cancer deaths were observed versus 6.31 expected [SMR, 1.27; 95%CI: 0.55–2.50].

Several other studies reviewed by Sivulka (2005) had mixed exposure to metallic nickel and other nickel compounds, and provide no evidence on the carcinogenicity of metallic nickel alone. Furthermore, many of the studies cited in the review involved mixed exposures in stainless steel welding and grinding, and manufacturing nickel alloys (Cox *et al.*, 1981; Enterline & Marsh, 1982; references from Tables 5 and 6 of Sivulka, 2005), and therefore were not considered relevant for evaluating the carcinogenicity of nickel and/or nickel compounds.

2.1.2 Cancer of the nasal cavity

Increased risks for nasal cancers were found to be associated with exposures during high-temperature oxidation of nickel matte and nickel-copper matte (roasting, sintering, calcining) in cohort studies in Canada, Norway (Kristiansand), and the United Kingdom (Clydach), with exposures in electrolytic refining in a study in Norway, and with exposures during leaching of nickel-copper oxides in acidic solution (copper plant), and extraction of nickel salts from concentrated solution (hydrometallurgy) in the United Kingdom (see Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-05-Table2.5.pdf).

In the Norwegian study, Andersen *et al.* (1996) demonstrated a dose–response relationship between both cumulative exposure to water-soluble nickel and nickel oxide compounds and the risk of nasal cancer. The SIR (compared to the general population) was the highest in the group of workers with the highest cumulative exposure to soluble nickel compounds combined with insoluble nickel compounds (SIR, 81.7; 95%CI: 45–135; based on 15 cases). For workers with the highest cumulative exposure to nickel oxide, the SIR was 36.6 (95%CI: 19.5–62.5; based on 13 cases) (see Table 2.6 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-05-Table2.6.pdf).

An update of nasal cancer in Finnish refinery workers after 20 years since the first exposure to nickel reported an SIR of 67.1 (95%CI: 12–242.0; based on two cases) (Anttila *et al.*, 1998). An additional nasal cancer was observed 2 years after the follow-up period ended, and a fourth potential nasal cancer (classified as a naso-pharyngeal cancer, 0.04 expected) was reported during the follow-up period. No nasal cancers were observed among the smelter workers who were exposed primarily to nickel matte, nickel subsulfide, nickel sulfides, and other metals.

Easton *et al.* (1992) attempted to identify the nickel compounds responsible for nasal cancer among 2524 Welsh nickel refinery workers employed for > 5 years before the end of 1969, and followed during 1931–85. As shown in Table 2.7, the risk for nasal cancer was in the range of 73–376 times the expected for those first employed before 1930, based on 67 nasal cancer deaths. A statistical model that fitted to the data on men whose exposures occurred before 1935, and that adjusted for age at first exposure, duration of exposure, and time since first exposure indicated that the soluble nickel effect on nasal cancer risk is the only one significant.

Table 2.7 Observed and expected deaths from nasal sinus cancer (1931–85) by year of first employment

Year first employed	Observed deaths	Expected deaths	SMR	95% CI
< 1920	55	0.15	376	276–477
1920–29	12	0.17	73	36–123
1930–39	1	0.07	14	0.4–80
1940–49	0	0.06	–	–
> 1950	0	0.06	–	–
Total	68	0.45	151	117–192

From Easton *et al.* (1992)

Grimsrud & Peto (2006) combined data from the most recent updates of Welsh nickel refinery workers to assess nasal cancer mortality risk by period of initial employment. For those first employed since 1930, an elevated risk was observed for nasal cancer (SMR, 8.70; 95%CI: 1.05–31.41, based on two observed deaths).

In one study of Swedish Ni–Cd battery workers, three nasal cancer cases versus 0.36 expected were observed (SIR, 8.32; 95%CI: 1.72–24.30) (Järup *et al.*, 1998). Two of these cases occurred among workers exposed to greater than 2 mg/m^3 nickel (SIR, 10.8; 95%CI: 1.31–39.0).

2.1.3 Other cancer sites

Other than for lung cancer and nasal sinus cancer, there is currently no consistency in the epidemiological data to suggest that nickel compounds cause cancer at other sites.

The results of several studies of workers exposed to nickel compounds showed a statistically elevated risk of a site-specific cancer in addition to lung and nasal cancer. A study of sinter plant workers in Canada showed a significantly elevated risk of cancer of the buccal cavity and pharynx (IARC, 1990). In a study in the Norwegian nickel-refining industry, a significant excess of laryngeal cancer was observed among roasting and smelter workers (Magnus *et al.*, 1982).

Stomach cancer was significantly elevated among men employed in a nickel- and chromium-plating factory in the United Kingdom (Burges, 1980). A study of men employed in a nickel-plating department (Pang *et al.*, 1996) showed a significant elevation in stomach cancer. Another study (Anttila *et al.*, 1998) demonstrated a significant excess of stomach cancer among nickel refinery workers.

A study of workers producing alloys with a high nickel content (Arena *et al.*, 1998) demonstrated a significant excess of colon cancer among 'non-white males' (relative risk, 1.92; 95%CI: 1.28–2.76), and a 2-fold risk of kidney cancer among white males employed in 'melting.' However, the excess risk was not associated with length of employment or time since first employment. [The Working Group noted that specific data was not provided in the article.]

A meta-analysis (Ojajärvi *et al.*, 2000) reported a significantly elevated risk for pancreatic cancer that upon further evaluation actually indicated no elevation in risk (Seilkop, 2002).

A population-based case–control study (Horn-Ross *et al.*, 1997) based on self-reported occupational exposure, showed a dose–response relationship between cumulative exposure to nickel compounds/alloys and salivary gland cancer. [The Working Group noted that the author corrected the direction of signs in Table 2 of her report in a subsequent erratum.]

2.2 Synthesis

The Working Group evaluated a large body of evidence and concluded that there is an elevated risk of lung and nasal sinus cancer among nickel refinery workers (IARC, 1990; Andersen *et al.*, 1996; Anttila *et al.*, 1998; Grimsrud & Peto, 2006), and an elevation in lung cancer risk among nickel smelter workers (IARC, 1990; Anttila *et al.*, 1998).

Epidemiological studies have provided evidence for lung cancer related to specific nickel compounds or classes of compounds (based, for example, on water solubility). Evidence for elevated risk of lung cancer in humans was demonstrated specifically for nickel chloride (Grimsrud *et al.*, 2003), nickel sulfate, water-soluble nickel compounds in general (Andersen *et al.*, 1996; Grimsrud *et al.*, 2002, 2003; Grimsrud *et al.*, 2005), insoluble nickel compounds, nickel oxides (Andersen *et al.*, 1996; Anttila *et al.*, 1998; Grimsrud *et al.*, 2003), nickel sulfides (Grimsrud *et al.*, 2002), and mostly insoluble nickel compounds (Andersen *et al.*, 1996).

A study that modelled risks of various nickel compounds and lung cancer risk identified both water-soluble nickel and metallic nickel as contributing to risk (Easton *et al.*, 1992). The largest study addressing worker exposure to metallic nickel (in combination with nickel oxide) showed a small but significant elevation in lung cancer risk (Arena *et al.*, 1998).

Other studies specifically addressing nickel metal exposures were uninformative and did not allow any judgment as to whether such exposures should be considered different with regard to cancer risk. It was not possible to entirely separate various nickel compounds in dose–response analyses for specific nickel compounds. In one analysis, an additional adjustment for water-soluble nickel compounds on risk of lung cancer indicated little association with cumulative exposure to sulfidic, oxidic or metallic nickel. One study of Ni–Cd battery workers exposed to nickel hydroxide and cadmium oxide demonstrated a significant risk of cancer of the nose and nasal sinuses.

On the basis of the Norwegian studies of refinery workers, the evidence is strongest for water-soluble nickel compounds and risk for lung cancer. The confidence of the Working Group in the above findings was reinforced by the availability of information on cigarette smoking for 89% of the Norwegian cohort, and the adjustments made for potential confounding exposures.

3. Cancer in Experimental Animals

Nickel and nickel compounds have been tested for carcinogenicity by intramuscular injection to rats, mice, and rabbits; by repository injections at multiple sites in hamsters, rabbits and mice; by intraperitoneal administration to rats and mice; and by intratracheal instillation, intrapleural, intrarenal, intraocular, inhalation, and subcutaneous exposure to rats.

Particularly relevant studies reviewed in the previous *IARC Monograph* (IARC, 1990) were reconsidered in this evaluation, and summarized in the text.

3.1 Oral administration

3.1.1 Nickel sulfide

In a 2-year multiple dose study, oral nickel sulfate hexahydrate given to male and female rats did not result in carcinogenesis (Heim *et al.*, 2007).

3.1.2 Nickel chloride

Nickel chloride was tested for carcinogenicity by oral administration in female hairless mice (CRL: SK1-hrBR). Mice were exposed to ultraviolet radiation (UVR) alone, nickel chloride alone (given in the drinking-water) and UVR + various concentrations of nickel chloride. Nickel

Table 3.1 Studies of cancer in experimental animals exposed to nickel compounds (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M, F) 104 wk Heim *et al.* (2007)	Nickel sulfate hexahydrate 0, 10, 30, 50 mg/kg/d (gavage),[a] 60/group/sex	Keratoacanthoma (tail): M–low dose 15% (numbers not provided)	$P < 0.001$	Age at start, 6 wk 99.9% pure Exposure-related decreased bw in males and females (2 highest dose groups) Exposure-related increased mortality ($P_{trend} < 0.008$) in high dose females but not males
Mouse, CRL: Sk1-hrBR (F) 224 d Uddin *et al.* (2007)	Nickel chloride in drinking-water at 3 wk of age 3 wk later UV treatment (1.0 kJ/m²) 3 d/wk for 26 wk Groups, number of animals Group 1: Controls, 5 Group 2: UV only, 10 Group 3: 500 ppm, 10 Group 4: UV + 20 ppm, 10 Group 5: UV + 100 ppm, 10 Group 6: UV + 500 ppm, 10 5–10/group	Skin (tumours): Number of tumours/mice at 29 wk Group 1: 0 Group 2: 1.7 ± 0.4 Group 3: 0 Group 4: 2.8 ± 0.9 Group 5: 5.6 ± 0.7 Group 6: 4.2 ± 1.0	Group 5 vs Group2 $P < 0.05$ Group 6 vs Group 2 $P < 0.05$	Age at start, 3 wk Nickel had no effect on growth of the mice Nickel levels in skin increased with dose

[a] vehicle not stated

d, day or days; F, female; M, male; UVR, ultraviolet radiation; vs, versus; wk, week or weeks

chloride alone did not cause skin tumours by itself, but when combined with UVR, it increased the UVR-induced skin tumour incidence (Uddin *et al.*, 2007).

See Table 3.1.

3.2 Inhalation exposure

3.2.1 Nickel sulfate hexahydrate

Nickel sulfate hexahydrate was not shown to be carcinogenic in male or female rats or male or female mice when given by inhalation in a 2-year bioassay study (Dunnick *et al.*, 1995; NTP, 1996a). Analysis of lung burden showed that nickel was cleared from the lungs (Dunnick *et al.*, 1995).

3.2.2 Nickel subsulfide

Nickel subsulfide induced lung tumours in rats exposed by inhalation (Ottolenghi *et al.*, 1975).

Inhalation of nickel subsulfide increased the incidence of alveolar/bronchiolar adenomas and carcinomas in male F344 rats, and increased combined lung tumours in females (Dunnick *et al.*, 1995; NTP, 1996b). Nickel subsulfide also increased the incidence of adrenal pheochromocytomas (benign or malignant) in male and female rats, malignant pheochromocytomas were increased in male rats. Significant dose-related trends were observed for both lung and adrenal tumours in both sexes.

3.2.3 Nickel oxide

The carcinogenicity of nickel oxide was investigated in 2-year inhalation studies in F344 male and female rats, and $B6C3F_1$ male and female mice. Nickel oxide induced tumours of the lung (alveolar bronchiolar adenomas or carcinomas), and adrenal medulla (malignant and benign pheochromocytoma) in both sexes of rats. Nickel oxide also increased the incidence of lung tumours in low-dose females but not in male mice (NTP, 1996c).

3.2.4 Metallic nickel

Inhaled metallic nickel increased the incidence of adrenal pheochromocytomas (benign, malignant, and benign and malignant combined) in male rats and adrenal cortex tumours in female rats (Oller *et al.*, 2008). Dose-related responses were observed for both types of adrenal tumours. No significant increases in lung tumours occurred. Elevated blood levels of nickel indicated that metallic nickel was bioavailable systematically after inhalation (Oller *et al.*, 2008).

3.2.5 Other forms of nickel

Nickel carbonyl induced lung carcinomas after inhalation exposure (Sunderman *et al.*, 1957, 1959).

See Table 3.2.

3.3 Parenteral administration

3.3.1 Nickel subsulfide

(a) Mouse

Nickel subsulfide induced local sarcomas after repository injections at multiple sites in numerous studies in mice (IARC, 1990).

No increase in lung tumour incidence was observed in male strain A/J mice, 20 or 45 weeks after exposure to various treatment regimens of nickel subsulfide (McNeill *et al.*, 1990). In another study, nickel subsulfide induced injection-site tumours in all three strains of mice, with the order of susceptibility to tumour formation being C3H, $B6C3F_1$, and C57BL6 (Rodriguez *et al.*, 1996). Waalkes *et al.* (2004, 2005) studied the carcinogenic response to nickel subsulfide in MT-transgenic and MT-null mice. Intramuscular administration of nickel subsulfide increased the incidence of injections-site tumours (primarily fibrosarcoma) in MT-transgenic and concordant wild-type mice, and lung tumours in MT-transgenic mice (Waalkes *et al.*, 2004). In MT-null mice and concordant wild-type mice, intramuscular injection of nickel sulfide induced fibrosarcomas as well (Waalkes *et al.*, 2005). MT-expression, either overexpression (MT-transgenic mice) or no expression (MT-null), did not significantly affect the carcinogenic response to nickel.

(b) Rat

Nickel subsulfide induced lung tumours in rats exposed by intratracheal instillation (Pott *et al.*, 1987). Intrarenal injection resulted in dose-related increases in renal cell tumours, and intraocular injection resulted in eye tumours in rats (Jasmin & Riopelle, 1976; Sunderman *et al.*, 1979; Albert *et al.*, 1982; Sunderman, 1983). Implantation of nickel subsulfide pellets into rat heterotropic tracheal transplant caused carcinomas and sarcomas (Yarita & Nettesheim, 1978). Local tumours were also observed in rats tested by intramuscular and intrarenal injection with nickel disulfide or nickel monosulfide (crystalline but not amorphous form), and in rats tested by intramuscular injection with nickel ferrosulfide matte (Sunderman, 1984; Sunderman *et al.*, 1984).

When administered by intrarenal injection to F344 male rats, nickel subsulfide induced renal sarcomas (Kasprzak *et al.*, 1994), which showed metastases to the lung, liver, and spleen. Injection site tumours (rhabdomyosarcoma,

Table 3.2 Studies of cancer in experimental animals exposed to nickel compounds or nickel powder (inhalation exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel sulfate hexahydrate				
Rat, F344 (M, F) 104 wk Dunnick *et al.* (1995), NTP (1996a)	0, 0.125, 0.25, 0.5 mg/m^3 (equivalent to 0, 0.03, 0.06, 0.11 mg nickel/m^3) for 6 h/d, 5 d/wk 63–65/group/sex	Lung (alveolar/bronchiolar adenomas or carcinomas or squamous cell carcinomas): M–2[a]/54, 0/53, 1/53, 3/53 F[b]–0/52, 0/53, 0/53, 1/54 Adrenal medulla (pheochromocytomas, benign or malignant[c]): M–16/54, 19/53, 13/53, 12/53 F–2/52, 4/52, 3/52, 3/54		Age at start, 6 wk 22.3% Nickel No treatment-related effects on survival. Mean bw of high-dose females were slightly lower than controls. Nickel lung burden values increased with increasing exposure (at 15 mo, 0.15–1.7 µg Ni/g lung)
Mouse, B6C3F$_1$ (M, F) 104 wk Dunnick *et al.* (1995), NTP (1996a)	0, 0.25, 0.5, 1.0 mg/m^3 (equivalent to 0, 0.06, 0.11, 0.22 mg nickel/ m^3) 6 h/d, 5 d/wk 63–65/group/sex	Lung (alveolar/bronchiolar adenomas or carcinomas): M–13/61, 18/61, 7/62, 8/61 F–7/61, 6/60, 10/60, 2/60		Age at start, 6 wk 22.3% Nickel No treatment-related effects on survival. Bw of high-dose males and all exposed female groups were decreased Nickel lung burden (µg Ni/g lung) below limit of detection at 7 and 15 mo interim evaluations

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel subsulfide				
Rat, F344 (M, F) 104 wk Dunnick *et al.* (1995), NTP (1996b)	0, 0.15, 1 mg/m^3 (equivalent to 0, 0.11, 0.73 mg nickel/m^3) 6 h/d, 5 d/wk 63/group/sex	Lung (alveolar/bronchiolar adenomas or carcinomas or squamous cell carcinomas): M–0/53, 6/53, 11/53 F–2/53, [a]6/53, 9/53	M: mid dose $P < 0.05$, high dose $P \leq 0.01$, $P_{trend} < 0.01$ F: mid dose $P \leq 0.05$ vs historical control, high dose $P < 0.05$, $P_{trend} < 0.05$	Age at start, 6 wk 73.3% Nickel No treatment-related effects on survival. Bw in high-dose groups Nickel lung burden increased with increasing exposure but reached steady-state by 15 mo (4–7 µg Ni/g lung). Lung carcinomas also were significantly increased in high-dose males
		Adrenal medulla (pheochromocytomas, benign or malignant): M–14/53, 30/53, 42/53 F–3/53, 7/53, 36/53	M: mid dose $P < 0.01$, high dose < 0.001, $P_{trend} < 0.001$ F: high dose, $P < 0.001$ $P_{trend} < 0.001$	
Mouse, B6C3F$_1$ (M, F) 104 wk Dunnick *et al.* (1995), NTP 1996b	0, 0.6, 1.2 mg/m^3 (equivalent to 0, 0.44, 0.9 mg nickel/m^3) 6 h/d, 5 d/wk 63/group	Lung (alveolar/bronchiolar adenomas or carcinomas): M–13/61; 5/59, 6/58 F–9/58, 2/59, 3/60	$P = 0.038N^h$ mid dose vs control $P = 0.028N^h$ mid dose vs control $P = 0.050N^h$ high dose vs control	Age at start, 6 wk 73.3% Nickel No treatment-related effects on survival. Mean bw lower in exposed groups than control group. Nickel lung burden increased with exposure concentration and with time (at 15 mo, 12–26 µg Ni/g lung)

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M, F) 78–80 wk + held 30 wk Ottolenghi *et al.* (1975)	Nickel subsulfide with or without 1 mo pre-exposure to the airborne system (clean air or nickel sulfide dust 0.97 ± 0.18 mg/m³ for 5 d/wk), followed by injection of hexachlorotetrafluorobutane to half the animals, thereafter the inhalation exposure was continued for all animals 16 exposure groups (8 groups/sex) Pre-exposure Inj. Controls: 29 (M), 28 (F) Inj. NiS: 29 (M), 28 (F) No Inj. Controls: 28 (M), 30 (F) No Inj. NiS: 22 (M), 26 (F) No Pre-exposure Inj. Controls: 32 (M), 32 (F) Inj. NiS: 24 (M), 32 (F) No Inj. Controls: 31 (M), 31 (F) No Inj. NiS: 32 (M), 26 (F)	Lung (adenomas, adenocarcinomas, squamous cell carcinomas, fibrosarcomas): NiS–17 (M), 12 (F) Controls–1 (M), 1 (F) Adrenal gland (hyperplasias and pheochromocytomas): NiS–12% Controls–1.1%	M, F: $P < 0.01$ $P < 0.01$	Pre-exposure: animals assigned airborne system for 1 mo No pre-exposure: animals housed in normal conditions for 1 mo Inj. = intravenous injection with pulmonary infraction agent Treatment-related decreased survival and decreased bw in males and females starting at 26 wk Inflammatory response – pneumonitis, bronchitis and emphysema Hyperplasias and squamous metaplasic changes in bronchial and bronchiolo-alveolar regions Infraction had no effect on carcinogenicity

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel oxide				
Rat, F344 (M, F) 104 wk Dunnick *et al.* (1995), NTP (1996c)	0, 0.62, 1.25, 2.5 mg/m^3 (equivalent to 0, 0.5, 1.0, 2.0 mg nickel/ m^3) 6 h/d, 5 d/wk 65/group/sex	Lung (alveolar/bronchiolar adenomas or carcinomas, or squamous cell carcinomas): M–1[a]/54, 1/53, 6/53, 4/52 F–1/53, 0/53[d], 6/53, 5/54	M, F: mid dose & high dose, $P \leq 0.05$ vs high dose	Age at start, 6 wk 76.6% Nickel No treatment-related effects on survival or bw Nickel lung burden increased with exposure and with time (at 15 mo, 262–1116 µg Ni/lung)
		Adrenal medulla (pheochromocytomas, benign or malignant): M–27/54, 24/53, 27/53, 35/54 F[e]–4/51, 7/52, 6/53, 18/54	M: high dose, $P = 0.027$, $P_{trend} = 0.008$ F: high dose, $P = 0.01$, $P_{trend} < 0.001$	If the squamous cell carcinomas (lung tumours) are not included, then the mid dose and high dose are significant vs the current controls Significantly increased incidence of malignant pheochromocytomas in high-dose males
Mouse, B6C3F$_1$ (M, F) 104 wk Dunnick *et al.* (1995), NTP (1996b)	0, 1.25, 2.5, 5.0 mg/m^3 (equivalent to 0, 1.0, 2.0, 3.9 mg nickel/m^3) 6 h/d, 5 d/wk ≈80/group/sex	Lung (alveolar/bronchiolar adenomas or carcinomas): M–9/57, 14/67, 15/66, 14/69 F–6/64, 15/66, 12/63, 8/64	F: low dose, $P \leq 0.01$	Age at start, 6 wk; 76.6% Nickel No treatment-related effects on survival or bw Nickel lung burden increased with exposure and with time (at 15 mo, 331–2258 µg Ni/lung)

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel metal powder				
Rat, Wistar Crl:Wi (G1XBRl/Han) (M, F) 12–30 mo Oller *et al.* (2008)	0, 0.1, 0.4, 1 mg/m^3 for 6 h/d, 5 d/wk, exposure time, additional hold time– Group 1: 0, 24 mo, 6 mo Group 2: 0.1, 24 mo, 6 mo Group 3, F: 0.4, 19 mo, 11 mo Group 3, M: 0.4, 24 mo, 6 mo Group 4, F: 1.0, ~14 mo, 0 mo Group 4, M: 1.0, ~12 mo, 0 mo 50/group	Groups 1, 2, 3 Adrenal gland (pheochromocytomas, benign or malignant): M–0/50, 5/50, 21/50 F–0/50, 5/49, 3/53 Adrenal cortex (adenomas or carcinomas): M–1/50, 3/50, 2/50 F–2/50, 2/49, 7/54	M: 0.4 mg/m^3 Significant increase for benign, malignant, benign combined, significant dose-related response[f] F: 0.4 mg/m^3 Significant increase for combined (adenoma and carcinoma) and significant dose-related response[f]	Age at start, 6 wk 99.9% pure Exposure-related mortality was observed in the high-dose group (Group 4 M, F, these animals were removed from the main study), and in Group 3 F (animals from satellite study reassigned to main study). Exposure-related bw effects were observed in Groups 2 (M), 3 (F &M), and 4 (F &M). Exposure-related lung toxicity was observed. Nickel lung burden (µg Ni/lung) increased with exposure and with time (appeared to reach steady-state at 12 mo)[g]. Increases in adrenal tumours were within published (external) historical controls for Wistar rats

[a] Includes 1 squamous cell carcinoma
[b] Only alveolar bronchiolar adenomas observed in female rats; adjusted rate not reported
[c] Adjusted rates not provided
[d] Dunnick reported 1 tumour and NTP technical report reported 0
[e] Only benign tumours observed.
[f] *P*-value not reported calculated by Peto
[g] Data not available for all time points
[h] A negative trend or a lower incidence in an exposure group is indicated by N
bw, body weight; d, day or days; h, hour or hours; F, female; M male; mo, month or months; Ni, nickel; NR, not reported; vs, versus; wk, week or weeks

fibromas, malignant fibrous histiocytomas or leiomyosarcomas) were observed in male or female F344 rats administered nickel subsulfide intramuscularly (Ohmori *et al.*, 1990; Kasprzak & Ward, 1991), and intra-articularly (Ohmori *et al.*, 1990). One study found that in female rats subjected to bone fractures and treated intramuscularly or intra-articularly had a shorter time to sarcoma formation, reduced survival time, and higher metastatic rate than rats treated with nickel alone (Ohmori *et al.*, 1990). Ohmori *et al.* (1999) studied strain susceptibility in male and female Wistar rats, and one strain (CRW) was found to be more sensitive to intramuscular injection of nickel.

(c) Hamster

Nickel subsulfide induced local sarcomas after repository injections at multiple sites in numerous studies in hamsters (IARC, 1990).

(d) Rabbit

Nickel subsulfide induced local sarcomas after repository injections at multiple sites in numerous studies rabbits (IARC, 1990).

3.3.2 Nickel oxide and hydroxide

Nickel oxide induced lung tumours in rats by intratracheal instillation (Pott *et al.*, 1987), local sarcomas in mice by intramuscular injection (Gilman, 1962), and rats by intramuscular, intrapleural, and intraperitoneal injection (Gilman, 1962; Sunderman & McCully, 1983; Skaug *et al.*, 1985; Pott *et al.*, 1987). Nickel hydroxide induced local sarcomas in rats when tested by intramuscular injection (Gilman, 1966; Kasprzak *et al.*, 1983).

Sunderman *et al.* (1990) tested the carcinogenicity of five nickel oxides or nickel-copper oxides in male Fisher 344 rats. The three oxides that induced sarcomas at the injection sites had measurable dissolution rates in body fluids, and were strongly positive in an erythrocytosis stimulation assay, demonstrating nickel bioavailability.

3.3.3 Nickel acetate

(a) Mouse

Nickel acetate when administered by intraperitoneal injection induced lung adenocarcinomas and pulmonary adenomas in Strain A mice (Stoner *et al.*, 1976; Poirier *et al.*, 1984).

(b) Rat

Nickel acetate induced malignant tumours in the peritoneal cavity when administered by intraperitoneal injection in rats (Pott *et al.*, 1989, 1990).

A single intraperitoneal injection of nickel acetate initiated renal epithelial tumours (including carcinoma) after promotion using sodium barbital in the drinking-water in male rats (Kasprzak *et al.*, 1990).

See Table 3.3.

3.3.4 Metallic nickel

Intratracheal administration of metallic nickel powder caused lung tumours in rats (Pott *et al.*, 1987). Metallic nickel also caused local tumours in rats when administered by injection (intrapleural, subcutaneous, intramuscular, and intraperitoneal) (Hueper, 1952, 1955; Mitchell *et al.*, 1960; Heath & Daniel, 1964; Furst & Schlauder, 1971; Berry *et al.*, 1984; Sunderman, 1984; Judde *et al.*, 1987; Pott *et al.*, 1987, 1990).

3.3.5 Nickel sulfate

Nickel sulfate induced malignant tumours in the peritoneal cavity when administered by intraperitoneal injection in rats (Pott *et al.*, 1989, 1990).

Table 3.3 Studies of cancer in experimental animals exposed to nickel compounds (parenteral administration and intratracheal instillation)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel subsulfide				
Mouse, Strain A (M) 45 wk McNeill *et al.* (1990)	i.t. and i.p. 0, 0.53, 0.160 mg/kg bw 3 dosing regimens for 15 wk 1/wk (15 treatments), 1 every 2 wk (8 treatments), 1 every 3 wk (5 treatments); 3 doses per regiment; 30/group 10 mice sacrified after 20 wk	Lung (adenomas at 45 wk[a]): i.t.– Number of treatments: dose 5: 68%, 63%, 58% 8: 64%, 54%, 61% 15: 47%, 47%, 56% i.p.– 5: 68%, 63%, 53% 8: 58%, 53%, 63% 15: 63%, 47%, 50%		Age at start, 8–10 wk Nickel subsulfide –1.8 µm mass medium diameter 73% Nickel and 26.3% sulfur (weight) Urethane (positive control) significantly increased tumour incidence i.p., i.t., after 20 wk, and i.t. after 45 wk, average. number of adenoma/mouse increased i.p. and i.t. at both time points No treatment effects on bw
Mouse, C57BL/6, $B6C3F_1$, CeH/He (M) 78 wk Rodriguez *et al.* (1996)	i.m. (thigh) 0, 0.5, 1.0, 2.5, 5.0, 10 mg/site (single injection) 30/group	Injection site (rhabdomyosarcomas, fibrosarcomas, and other e.g. liposarcomas, haemangiosarcomas): C3He 0/30, 5/30 (16.6%), 10/30 (33.3%), 20/27 (74.1%), 28/29, (96.6%) 14/14 (100%) $B6C3F_1$ 0/30, 2/29 (6.9%), 8/30 (26.7%), 15/30 (50.0%), 16/20 (80%), 5/6 (83.3%) C57BL 0/24, 1/27 (3,7%), 4/28 (14.3%), 6/21 (28.6%), 6/15(40%), 0/2	[$P = 0.052$, 0.5 mg; $P < 0.001$ for other doses][a] [$P < 0.01$, 1.0 mg, $P < 0.001$, 2.5, 5.0, 10 mg][a] [$P < 0.01$, 2.5, 5 mg][a]	Age at start, 6–8 wk; weight, 23–29 g High dose was lethal within 1 wk to over 50% of all 3 strains; susceptibility was C57BL > B6C3F1 > C3H Treatment-related decrease in bw was observed for C3H and $B6C3F_1$ at 2 highest doses. Tumours of the liver, lung adenomas and leukaemias were also observed, but were not increased in exposed groups compared to controls Susceptibility to tumours C3H > $B6C3F_1$ > C57BL

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, MT transgenic and wild-type (M) 104 wk Waalkes *et al.* (2004)	i.m. (both thighs) 0, 0.5, 1 mg/site (single injection) 25/group	Injection site (primarily fibrosarcomas, but also included fibromas and lymphosarcomas): WT–0/24, 5/25 (20%), 10/25 (40%) MT-Tg–0/25, 7/25 (28%), 7/24 (29%) Lung (adenomas or adenocarcinomas): WT–6/24 (25%), 5/25 (20%), 9/25 (36%) MT-Tg–0/25, 3/25 (12%), 4/24 (17%)	WT: $P < 0.05$, mid-and low dose, $P_{trend} < 0.0001$ MT-Tg: $P < 0.05$, mid-and low dose, $P_{trend} = 0.0081$ trend MT-Tg: $P = 0.0502$ high dose $P_{trend} = 0.046$	Age at start, 12 wk 99.9% pure, 30 µm particles Average survival time less in MT-Tg mice than controls. Treatment-related decrease in survival in WT but not MT-Tg mice. No effect on bw No differences in injection-site tumour incidence or latency between MT-Tg and WT mice MT-transgenic controls had significantly lower incidence of lung tumours than WT controls.
Mouse, MT-null (double knockout) and wild-type (M) 104 wk Waalkes *et al.* (2005)	i.m. (both thighs) 0, 0.5, 1 mg/site (single injection), 25/group	Injection site (primarily fibrosarcomas, but also included fibromas): WT–0/24, 8/25(32.0%), 18/25 (72.0%) MT-null–0/24, 11/24 (45.8%), 15/23 (62.5%) Lung (adenomas or adenocarcinomas): WT–7/24 (29.2%), 12/25 (48.0%), 11/25 (44.0%) MT-null–10/24 (41.7%), 13/24 (54.2%), 4/23 (16.7%)	$P < 0.05$ low and high dose $P < 0.05$ low and high dose	Age at start, 12 wk 99.9% pure, < 30 µm particles No difference in survival between control MT-null mice and control WT mice. Nickel treatment reduced survival at later time points corresponding to the appearance of sarcomas. Nickel treatment reduced bw in high-and mid dose MT-null and high-dose WT mice

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, MT-null (double knockout) and wild-type (M) 104 wk Waalkes *et al.* (2005) (contd.)		Lung (adenocarcinomas): WT–1/24 (4.2%), 10/25 (40.0%), 3/25 (12.0%) MT-null–3/24 (12.5%), 3/24 (12.5%), 4/23 (17.4%)	WT: $P < 0.05$ low dose	
		Lung (adenomas): WT–6/24 (25%), 2/25 (8.0%), 8/25 (32.0%)		
		MT-null–7/24 (29.2%), 10/24 (41.7%), 0/23	MT-null: $P < 0.05$ control vs high dose	
Rat, F344/NCr (M) 109 wk Kasprzak *et al.* (1994)	i.r. (2 injections) Ni_3S_2 – 5 mg, MgCarb –6.2 mg, Fe^0–3.4 mg Groups: treatment, number of animals Group 1: Ni_3S_2, 40 Group 2: Ni_3S_2 + MgCarb, 20 Group 3: MgCarb, 20 Group 4: Ni_3S_2+ Fe^0, 20 Group 5: Fe^0, 20 Group 6: vehicle, 20 20–40/group	Kidney (malignant tumours of mesenchymal cell origin) at 104 wk: Group 1: 25/40 (63%) Group 2: 4/20 (20%) Group 3: 0/20 Group 4: 12/20 (60%) Group 5: 0/20 Group 6: 0/20	Group 2 vs Group 1 [$P < 0.01$][a]	Ni_3S_2 < 10µm No effect on bw or survival (from causes other than kidney tumours) MgCarb also delayed onset of tumours (besides decreasing the incidence), and Fe decreased time until first tumour Metastases to lung, liver, spleen and other kidney

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344/NCr (M) 109 wk Kasprzak & Ward (1991)	i.m. and s.c (single injection) Ni_3S_2– 2.5 mg, MB – 0.5 mg, CORT–1.0 mg, IND –1.0 mg. Groups: i.m., s.c., number of animals Group 1: Ni_3S_2, none, 20 Group 2: MB, none, 20 Group 3: Ni_3S_2+ MB, none, 20 Group 4: CORT, none, 20 Group 5: Ni_3S_2+ CORT, none, 20 Group 6: IND, none, 20 Group 7: Ni_3S_2+ IND, none, 20 Group 8: water, none, 20 Group 9: Ni_3S_2, MB, 20 Group 10: Ni_3S_2, IND, 20 20/group	Injection-site tumours (rhabdomosarcomas, fibrosarcomas, histolytic sarcomas): 36 wk; 71 wk Group 1: 10/20 (50%); 17/20 (85%) Group 2: 0/20; 0/20 Group 3:0/20; 1/20 (5%) Group 4: 0/20; 0/20 Group 5: 9/20 (45%); 17/20 (85%) Group 6: 0/20; 0/20 Group 7: 6/20 (30%); 16/20 (80%) Group 8: 0/20; 0/20 Group 9: 18/20 (90%); 20/20 (100%) Group 10: 13/20 (65%); 19/20 (95%)	[Groups 2, 3, 4, 6 or 8 vs Group 1, 36 & 71 wk, $P < 0.01$; Group 9 vs Group 1, 36 wk, $P < 0.05$][a]	Age at start, 8 wk Ni_3S_2 < 10μm No effect on bw Metastases to the lung MB given away from the injection site (s.c.) decreased tumour latency induced by Ni_3S

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (F) 1 yr Ohmori *et. al.* (1990)	Ni_3S_2–10 mg Groups, treatment, number of animals Group 1: fracture bone, 10 mg/fracture, 20 Group 2: 10 mg i.m right thigh, 20 Group 3: 10 mg i.a. right knee joint, 20 Group 4: control (CM), 3 fractured bone, 3 i.m., 2 i.a. 20/group	Injection site (malignant fibrous histiocytomas, rhabdomyosarcomas, fibrosarcomas, leiomyosarcomas): Group 1: 17/20 (85%) Group 2: 20/20 (100%) Group 3: 16/20 (80%) Group 4: 0/7 (0%) Metastasis (lymph node, lung): Group 1: 16/17 (94.1), 9/17 (52.9) Group 2: 5/20 (25.0%), 3/20 (15.0%) Group 3: 3/16 (18.8%), 2/16 (12.5%) Group 4: 0/7, 0/7	$P < 0.05$, Group 1 vs Group 2 or Group 3	Age at start, 10 wk Ni_3S_2 medium particle diameter < 2μm Vehicle, CM Tumour-induction time and survival time shorter in Group 1 than Groups 2 or 3. No osteogenic sarcoma developed in bone-fracture group
Rat, Wistar (M, F) 70 wk Ohmori *et al.* (1999)	Ni_3S_2–10 mg i.m. (single injection) Groups, strain, treatment; number of animals Group 1: SHR–10 mg; 15F, 15M Group 2: CWR–10 mg; 15F, 16M Group 3: SHR–0 mg; 6F, 6M Group 4: CWR–0 mg 7F, 7M 6–15/group	Sarcomas (rhabdomyosarcomas, leiomyosarcomas, fibrosarcomas and malignant fibrous histiocytomas): Groups: F; M; Total Group 1: 2/15 (13.3%); 5/15 (33.3%); 7/30 (23.3%) Group 2: 8/15 (53.3%), 13/16 (81.4%); 21/31 (67.7%) Group 3: 0/6, 0/6 Group 4: 0/7, 0/7	Total: Group 1 vs Group 2, $P < 0.005$	Age, 10 wk Ni_3S_2 medium particle diameter < 2μm Vehicle, CM Tumour incidence, progression (as shown by tumour size and metastasis) was significantly lower in SHR rats (M, F combined) than in CWR rats Metastases observed in the lung and lymph node

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel oxide				
Rat, F344 (M) 104 wk Sunderman *et al.* (1990)	i.m. (hind limb) single injection Group: Ni by wt.; other elements V: vehicle control (glycerol) A: 0.81% Ni (III); none B: 0.05% Ni (III); none F: < 0.03% Ni (III); none H: 21% Cu, 2% Fe, 1.1% Co, 1% S, 0.5% Ni_3S_2 I: 13% Cu, 1.2% Fe, 1.0 Co, 0.3% S, 1.0% Ni_3S_2 (positive control) 20 mg Ni/rat 15/group	Injection site (rhabdomyosarcomas, fibrosarcomas, malignant fibrous histiocytomas, leiomyosarcomas, undifferentiated): V, 0/15; A, 6/15 (40.0%); B, 0/15; F, 0/15; H, 13/15 (86.7%); I, 15/15 (100%) Positive control, Ni_3S_2 15/15(100%) **Metastases** V: 0, A: 3; B: 0; F: 0; H: 4; I: 4 Ni_3S_2: 12 **Other primary tumours** V: 0; A: 0; B: 3; F: 0; H: 0; I: 3 Ni_3S_2: 0	$P < 0.01$ A; $P < 0.001$ H, I, Ni_3S_2	Age at start, ~2 mo 5 NiO compounds – all compounds had 52–79% Nickel (total), and 22–24% O. Nickel could not be determined in Groups H and I because of the presence of sulfur Groups A, H, and I all had measurable dissolution rates in body fluids and were strongly positive in an erythrocytosis-stimulation assay Compounds B and F were insoluble in body fluids, did not stimulate erythrocytosis and had little Ni (III), Cu Fe, Co, or S
Rat, Wistar (F) Life span Pott *et al.* (1987)	(mg x wk) number of animals NiO 50 mg (10 × 5); 34 150 mg (10 × 15); 37 Ni_3S_2 0.94 mg (15 × 0.063); 47 1.88 mg (15 × 0.125); 45 3.75 mg (15 × 0.25); 47 Nickel powder 6 mg (20 × 0.3); 32 9 mg (10 × 0.9); 32 32–47/group	Lung (adenomas, adenocarcinomas, squamous cell carcinomas): % tumours for each dose NiO–27%, 31.6% Ni_3S_2–15%, 28.9% Nickel powder–25.6%, 25% Saline, 0%		Age at start, 11 wk NiO, 99.9% pure

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel acetate				
Rat, F344/NCr (M) 101 wk Kasprzak *et al.* (1990)	NiAcet –90 µmol/kg bw single i.p. injection NaBB–50 ppm in drinking-water (2 wk after NiAcet) Groups, treatment, # of animals Group 1: NiAcet, 23 Group 2: NiAcet + NaBB, 24 Group 3: NaBB, 24 Group 4: Saline, 24 24/group	Renal cortical tumours (adenomas & adenocarcinomas): Group 1–1/23 (4.3%) Group 2–16/24 (66.7%) (4 carcinomas) Group 3–6/24 (25%) Group 4–0/24 Renal pelvic tumours (papillomas & carcinomas): Group 1–0/23 Group 2–8/24 (33.3%) Group 3–13/24 (54.2%) (1 carcinoma) Group 4–0/24	$P < 0.008$ vs Group 3	Age at start, 5 wk Initiation/promotion study Decreased survival and bw in rats given nickel acetate followed by NaBB Kidney weight increased in Groups 2 and 3 Renal cortical tumours: metastatic nodules observed in the lung, spleen and liver
Mouse, Strain A (M, F) 30 wk Stoner *et al.* (1976)	i.p. Nickel acetate 3×/wk (24 injections total) 0, 72, 180, 360 mg/kg Saline control 20/group	Lung (adenomas): Average number of tumours/mouse (mean ± SD) Saline: 0.42 ± 0.10 72: 0.67 ± 0.16 180: 0.71 ± 0.19 360: 1.26 ± 0.29	$P < 0.01$ high dose	Age at start, 6–8 wk 99.9% pure Sample of nodules confirmed by histopathology No difference in control M, F, so M, F were combined Positive control urethane Control saline Doses correspond to MTD, ½ MTD, 1/5 MTD
Mouse, Strain A (M, F) 30 wk Poirier *et al.* (1984)	i.p. Nickel acetate 10.7 mg/kg bw (0.04 mmol kg/bw)/injection 3×/wk (24 injections total) 30/group/sex	Lung (adenomas): Average number of tumours/mouse (mean ± SD) Saline: 0.32 ± 0.12 Nickel acetate: 1.50 ± 0.46	$P < 0.05$	Age at start, 6–8 wk Nodules (sample) confirmed by histology Co-exposure to calcium and magnesium decreased multiplicity

[a] Calculated by Fisher Exact Test, Significance not reported by authors

bw, body weight; CM, chloromycetin; CORT, cortisol; CWR, common closed colony rats; F, female; Fe^0, metallic iron; HSR, spontaneously hypertensive rats; i.a., intra-articular; i.f., intra-fat; i.m., intramuscular; IND, indometacin; i.p., intraperitoneal; i.r., intrarenal; i.t., intratracheal instillation; M, male; MB, *Mycobacterium bovis* antigen; MgCarb, magnesium basic carbonate; MT, metallothionien; MTD, maximum tolerated dose; NABB, sodium barbital; Ni, nickel; NiAcet, nickel acetate; Ni_3S, nickel subsulfide; s.c., subcutaneous; SD, standard deviation; Tg, Transgenic; wk, week or weeks; WT, wild type; yr, year or years

Table 3.4 Studies of cancer in experimental animals exposed to nickel acetate (transplacental exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Results Target organs	Significance	Comments
Rat, F344/NCr (M, F) 85 wk Diwan *et al.* (1992)	*Dams – i.p* NiAcet (90 µmol/kg wt total) Group:/µmol/kg bw; regimen Group 1: 90; once at Day 17 of gestation Group 2: 45; twice at Days 16 & 18 of gestation Group 3: 45; 4 times at Days 12, 14, 16, 18 of gestation Group 4: control (180 NaAcet) once at Day 18 of gestation *Offspring 4 to 85 wk (drinking-water)* ad libitum 1A, 2A, 4A – tap water 1B, 2B, 4B – 0.05% NBB	Renal tumours (cortex adenomas and carcinomas; or pelvis papillomas and carcinomas): 1A: 0/17 (M), 0/16 (F) 2A: 0/15 (M), 0/15 (F) 4A: 0/15 (M), 0/16 (F) 1B: 8/15 (53.3%, M), 0/15 (F) 2B: 7/15 (46.7%, M), 0/15 (F) 4B: 1/15 (6.67%, M), 0/14 (F) Pituitary gland (adenomas or carcinomas): 1A: 9/17 (52.9%, M), 5/16 (31.3%, F), 14/33 (42.3%, M, F) 2A: 6/15 (40.0%, M), 8/16 (50%, F), 14/31 (45.2%, M, F) 4A: 1/15 (6.7%, M), 3/14 (21.4%, F) 1B: 6/15 (40.0%, M), 5/15 (33.3%, F) 2B: 7/15 (46.7%, M), 6/15 (40.0%, F) 4B: 2/15 (13.3%, M), 4/14 (28.6%, F)	M: $P = 0.007$ (1B vs 4B) M: $P = 0.012$ (2B vs 4B) M, F: $P = 0.12$ 1A vs 4A M, F: $P = 0.008$ 2A vs 4A	Dams, age at start 3–4 mo Purity not provided Male (Groups 1 & 2) – significantly decreased bw at 75 wk All offspring in Group 3 died at 72 h. Survival was decreased in Groups 1A, 1B, 2A and 2B compared to controls (4A and 4B) Pituitary tumours: significantly decreased latency for Groups 1A (M, F), 1B (M, F) and 2A (F) compared to the Groups 4A or 4B (corresponding M or F)

h, hour or hours; F, female; i.p., intraperitoneal; M, male; mo, month or months; NaBB, sodium barbital; vs, versus; wk, week or weeks

3.3.6 Nickel chloride

Nickel chloride induced malignant tumours in the peritoneal cavity when administered by intraperitoneal injection in rats (Pott *et al.*, 1989, 1990).

3.3.7 Other forms of nickel

Intramuscular administration of nickel sulfarsenide, nickel arsenides, nickel antimonide, nickel telluride, and nickel selenides caused local sarcomas in rats (Sunderman & McCully, 1983). Intramuscular administration of nickelocene caused some local tumours in rats and hamsters (Furst & Schlauder, 1971).

3.4 Transplacental exposure

3.4.1 Nickel acetate

Diwan *et al.* (1992) studied the carcinogenic effects of rats exposed transplacentally to nickel acetate and postnatally to sodium barbital in drinking-water. Pregnant F344 were given nickel acetate by intraperitoneal injection, and their offspring were divided into groups receiving either tap water or sodium barbital in drinking-water. An increased incidence in pituitary tumours was observed in the offspring of both sexes transplacentally exposed to nickel acetate. These tumours were mainly malignant, and are rare tumours. Renal tumours were observed in the male offspring exposed transplacentally to nickel acetate, and receiving sodium barbital postnatally, but not in the male offspring receiving tap water after nickel *in utero*.

See Table 3.4.

3.5 Synthesis

The inhalation of nickel oxide, nickel subsulfide, and nickel carbonyl caused lung tumours in rats. Intratracheal instillation of nickel oxide, nickel subsulfide, and metallic nickel caused lung tumours in rats. Lung tumours were observed by the intraperitoneal injection of nickel acetate in two studies in A/J mice, and by intramuscular injection of nickel subsulfide in mice. The inhalation of nickel oxide, nickel subsulfide, and metallic nickel caused adrenal medulla pheochomocytoma in rats. Transplacental nickel acetate induced malignant pituitary tumours in the offspring in rats. Several nickel compounds (nickel oxides, nickel sulfides, including nickel subsulfide, nickel sulfate, nickel chloride, nickel acetate, nickel sulfarsenide, nickel arsenide, nickel antimonide, nickel telluride, nickel selenide, nickelocene, and metallic nickel) administered by repository injection caused sarcomas in multiple studies. The inhalation of metallic nickel did not cause lung tumours in rats. The inhalation and oral exposure to nickel sulfate did not cause tumours in rats or mice. The inhalation of nickel subsulfite did not cause tumours in mice.

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

In rodents, nickel salts and nickel sulfides are absorbed through the lungs and excreted mainly in the urine (Benson *et al.*, 1994, 1995a). After inhalation exposure to green nickel oxide, nickel is not distributed in extrapulmonary tissues, and is excreted only in faeces (Benson *et al.*, 1994). In humans, soluble nickel compounds are rapidly absorbed through the lungs, and excreted in the urine. After inhalation exposure to insoluble nickel species, elevated concentrations of nickel are observed in the plasma and urine, but the absorption is slow (Bernacki *et al.*, 1978; Tola *et al.*, 1979).

In rats exposed to nickel sulfate hexahydrate by inhalation for 6 months or 2 years,

no pulmonary accumulation is observed; in a similar exposure scenario with nickel subsulfide, concentrations of nickel are detected in the lungs, with very slight nickel accumulation. Following the exposure of green nickel oxide to rats, the nickel lung clearance half-life is approximately 130 days, and in long-term exposure (NTP, 1996a, b, c; described in Section 3), a remarkable accumulation of nickel is observed (Benson *et al.*, 1995b; Dunnick *et al.*, 1995). The lung clearance half-life of nanoparticulate black nickel oxide in rats is reported as 62 days (Oyabu *et al.*, 2007). The difference in the two clearance rates may be related to the greater water solubility (and the smaller particle size) of the nanoparticulate black nickel oxide. In mice, the observed clearance for nickel sulfate is fast, but for nickel subsulfide intermediate and for green nickel oxide, very slow (Dunnick *et al.*, 1995).

4.1.1 Cellular uptake

Nickel chloride has been shown in different cell lines in culture to be transported to the nucleus (Abbracchio *et al.*, 1982; Edwards *et al.*, 1998; Ke *et al.*, 2006, 2007; Schwerdtle & Hartwig, 2006). Soluble nickel chloride compounds enter cells via the calcium channels and by metal ion transporter 1 (Refsvik & Andreassen, 1995; Funakoshi *et al.*, 1997; Gunshin *et al.*, 1997; Garrick *et al.*, 2006). Crystalline nickel sulfides are phagocytized by a large variety of different cells in culture (Kuehn *et al.*, 1982; Miura *et al.*, 1989; Hildebrand *et al.*, 1990, 1991; IARC, 1990).

Black nickel oxide and nickel chloride are taken up by human lung carcinoma cell lines A549 in culture; the nucleus/cytoplasm ratio is > 0.5 for black nickel oxide, and < 0.18 for nickel chloride (Fletcher *et al.*, 1994; Schwerdtle & Hartwig, 2006).

After phagocytosis of nickel subsulfide, intracellular nickel containing particles rapidly dissolve, and lose sulfur (Arrouijal *et al.*, 1990; Hildebrand *et al.*, 1990, 1991; Shirali *et al.*, 1991).

4.2 Genetic and related effects

The mechanisms of the carcinogenicity of nickel compounds have been reviewed extensively (Hartwig *et al.*, 2002; Zoroddu *et al.*, 2002; Costa *et al.*, 2003, 2005; Harris & Shi, 2003; Kasprzak *et al.*, 2003; Lu *et al.*, 2005; Durham & Snow, 2006; Beyersmann & Hartwig, 2008; Salnikow & Zhitkovich, 2008).

Based on the uptake and distribution in cells described above, the ultimate genotoxic agent is Ni (II). However, direct reaction of Ni (II) with DNA does not seem to be relevant under realistic exposure conditions. Nevertheless, nickel is a redox-active metal that may, in principle, catalyse Fenton-type reactions, and thus generate reactive oxygen species (Nackerdien *et al.*, 1991; Kawanishi *et al.*, 2001). Genotoxic effects have been consistently observed in exposed humans, in experimental animals, and in cell culture systems, and include oxidative DNA damage, chromosomal damage, and weak mutagenicity in mammalian cells. These effects are likely to be due to indirect mechanisms, as described in detail below.

4.2.1 Direct genotoxicity

(a) DNA damage

Water-soluble as well as water-insoluble nickel compounds induce DNA strand breaks and DNA protein crosslinks in different mammalian test systems, including human lymphocytes. Nevertheless, in the case of DNA strand breaks and oxidative DNA lesions, these events mainly occur with conditions that involve comparatively high cytotoxic concentrations (IARC, 1990; Pool-Zobel *et al.*, 1994; Dally & Hartwig, 1997; Cai & Zhuang, 1999; Chen *et al.*, 2003; M'Bemba-Meka *et al.*, 2005; Schwerdtle & Hartwig, 2006; Caicedo *et al.*, 2007). This is also true for the induction of oxidative DNA base modifications in cellular systems. Nevertheless, oxidative DNA damage is also observed in experimental animals, this may

be due to repair inhibition of endogenous oxidative DNA damage.

The intratracheal instillation of several soluble and insoluble nickel compounds to rats significantly increases 8-hydroxydeoxyguanine (8-OH-dG) content in the lungs. Concomitantly, microscopic signs of inflammation in the lungs are also observed. Two distinct mechanisms are proposed: one via an inflammatory reaction and the other through cell-mediated reactive oxygen species formation (Kawanishi *et al.*, 2001; Kawanishi *et al.*, 2002).

(b) Chromosomal alterations

Water-soluble and poorly water-soluble nickel compounds induce sister chromatid exchange and chromosomal aberrations at toxic levels in different mammalian test systems (Conway *et al.*, 1987; Conway & Costa, 1989; IARC, 1990; Howard *et al.*, 1991). Chromosomal aberrations are most pronounced in heterochromatic chromosomal regions (Conway *et al.*, 1987). Water-soluble and poorly water-soluble nickel compounds induce micronuclei at comparatively high concentrations. Because increases in both kinetochore-positive and -negative micronuclei are observed, these effects are likely due to aneugenic as well as clastogenic actions (Arrouijal *et al.*, 1990, 1992; Hong *et al.*, 1997; Seoane & Dulout, 2001). The induction of chromosomal aberrations and micronuclei in rodents treated with different nickel compounds is not consistent across studies (Sobti & Gill, 1989; Arrouijal *et al.*, 1990; Dhir *et al.*, 1991; IARC, 1990; Oller & Erexson, 2007). Enhanced frequencies of chromosomal aberrations were observed in some studies in lymphocytes of nickel-exposed workers (IARC, 1990).

(c) Gene mutations in bacterial and mammalian test systems

Nickel compounds are not mutagenic in bacterial test systems, and are only weakly mutagenic in cultured mammalian cells. Even though, mutagenic responses for both water-soluble and water-insoluble nickel compounds have been reported in transgenic G12 cells, this effect was later shown to result from epigenetic gene-silencing (Lee *et al.*, 1995). Nevertheless, the prolonged culture of V79 cells after treatment with nickel sulfate results in the appearance of genetically unstable clones with high mutation rates together with chromosomal instability (Little *et al.*, 1988; Ohshima, 2003).

(d) Cell transformation

Water-soluble and poorly water-soluble nickel compounds induced anchorage-independent growth in different cell systems (IARC, 1990), including the mouse-embryo fibroblast cell-line PW and the human osteoblast cell line HOS-TE85 (Zhang *et al.*, 2003). Nickel compounds were shown to cause morphological transformation in different cell types (Conway & Costa, 1989; Miura *et al.*, 1989; Patierno *et al.*, 1993; Lin & Costa, 1994).

4.2.2 Indirect effects related to genotoxicity

As stated above, the direct interaction of nickel compounds with DNA appears to be of minor importance for inducing a carcinogenic response. However, several indirect mechanisms have been identified, which are discussed below.

(a) Oxidative stress

Treatment with soluble and insoluble nickel causes increases in reactive oxygen species in many cell types (Huang *et al.*, 1993; Salnikow *et al.*, 2000; Chen *et al.*, 2003).

Increased DNA stand breaks, DNA–protein crosslinks and sister chromatid exchange are found in cells treated with soluble and insoluble nickel compounds, and these are shown to result from the increase in reactive oxygen species (Chakrabarti *et al.*, 2001; Błasiak *et al.*, 2002; Woźniak & Błasiak, 2002; M'Bemba-Meka *et al.*, 2005, 2007).

Intraperitoneal injection of nickel acetate in rat did not cause any DNA damage in liver and kidney at 12 hours. However, oxidative DNA damage increased after 24 hours, and persisted in the kidney for 14 days (Kasprzak *et al.*, 1997).

(b) Inhibition of DNA repair

The treatment of cells with soluble Ni (II) increases the DNA damage and the mutagenicity of various agents (Hartwig & Beyersmann, 1989; Snyder *et al.*, 1989; Lee-Chen *et al.*, 1993).

Soluble Ni (II) inhibits nucleotide-excision repair after UV irradiation, and the effect seems to be on the incision, the polymerization, and ligation steps in this pathway (Hartwig *et al.*, 1994; Hartmann & Hartwig, 1998; Woźniak & Błasiak, 2004). One of the proteins in nucleotide-excision repair, the XPA protein, may be a target of Ni (II) (Asmuss *et al.*, 2000a, b).

Soluble nickel chloride also inhibits base-excision repair. The base-excision repair enzyme, 3-methyladenine-DNA glycosylase II, is inhibited specifically (Dally & Hartwig, 1997; Woźniak & Błasiak, 2004; Wang *et al.*, 2006).

There is some evidence that the enzyme O^6-methylguanine-DNA methyltransferase (MGMT) is inhibited by nickel chloride (Iwitzki *et al.*, 1998).

(c) Epigenetic mechanisms

Both water-soluble and water-insoluble nickel compounds are able to cause gene silencing (Costa *et al.*, 2005). This effect was first found when "mutations" in the transgenic *gpt* gene in G12 cells were found to be epigenetically silenced rather than mutated (Lee *et al.*, 1995). Genes that are located near heterochromatin are subject to such inactivation by nickel. The *gpt* gene was silenced by DNA methylation. Additional studies show that cells treated with nickel have decreased histone acetylation, and altered histone methylation patterns (Golebiowski & Kasprzak, 2005; Chen *et al.*, 2006). Nickel also causes ubiquination and phosphorylation of histones (Karaczyn *et al.*, 2006; Ke *et al.*, 2008a, b). Permanent changes in gene expression are important in any mechanism of carcinogenesis.

4.3 Synthesis

The ultimate carcinogenic species in nickel carcinogenesis is the nickel ion Ni (II). Both water-soluble and poorly water-soluble nickel species are taken up by cells, the former by ion channels and transporters, the latter by phagocytosis. In the case of particulate compounds, nickel ions are gradually released after phagocytosis. Both water-soluble and -insoluble nickel compounds result in an increase in nickel ions in the cytoplasm and the nucleus. Nickel compounds are not mutagenic in bacteria, and only weakly mutagenic in mammalian cells under standard test procedures, but can induce DNA damage, chromosomal aberrations, and micronuclei *in vitro* and *in vivo*. However, delayed mutagenecity and chromosomal instability are observed a long time after treatment of cells with nickel. Nickel compounds act as co-mutagens with a variety of DNA-damaging agents. Thus, disturbances of DNA repair appear to be important. A further important mechanism is the occurrence of epigenetic changes, mediated by altered DNA methylation patterns, and histone modification. Inflammation may also contribute to nickel-induced carcinogenesis.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of mixtures that include nickel compounds and nickel metal. These agents cause cancers of the lung and of the nasal cavity and paranasal sinuses.

There is *sufficient evidence* in experimental animals for the carcinogenicity of nickel monoxides, nickel hydroxides, nickel sulfides (including

nickel subsulfide), nickel acetate, and nickel metal.

There is *limited evidence* in experimental animals for the carcinogenicity of nickelocene, nickel carbonyl, nickel sulfate, nickel chloride, nickel arsenides, nickel antimonide, nickel selenides, nickel sulfarsenide, and nickel telluride.

There is *inadequate evidence* in experimental animals for the carcinogenicity of nickel titanate, nickel trioxide, and amorphous nickel sulfide.

In view of the overall findings in animals, there is *sufficient evidence* in experimental animals for the carcinogenicity of nickel compounds and nickel metal.

Nickel compounds are *carcinogenic to humans (Group 1).*

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